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HACETTEPE ROMATOLOJİ DERNEĞİ 2016

7. Ankara Romatoloji Yılsonu Buluşması

16-18 Aralık 2022

Sheraton Ankara Hotel

HUVAM
Hacettepe Üniversitesi Vaskülit Tanı ve Tedavi Uygulama ve Araştırma Merkezi

Hacettepe Üniversitesi Vaskülit Tanı ve
Tedavi Uygulama ve Araştırma Merkezi
&
Hacettepe Romatoloji Derneği Ortak Programı

**Chapel Hill Konsensüsü Konferansında Yer Alan
Ancak Az Konuşulan Vaskülitler:
Nedir? Ne Değildir? Gerçek yaşamdan olgu örnekleri**

16 Aralık 2022, Cuma

Saat	Konu	Konuşmacılar	Oturum Başkanları
13:00-14:30	**1.OTURUM**		
13:00-13:15	Chapel Hill 2011 & Chapel Hill Kutanöz Vaskülitler Güncellemesi	Ömer Karadağ	Haner Direskeneli, Gökhan Keser
13:15-13:30	Primer MSS Vasküliti? Nedir? Ne Değildir? Olgu sunumu	Veli Yazısız Tahir Saygın Öğüt	
13:30-13:45	Romatoid vaskülit Nedir? Ne Değildir? Olgu Sunumu	Ayten Yazıcı Özlem Özdemir Işık	
13:45-14:00	Lupus Vasküliti Nedir? Ne Değildir? Olgu Sunumu	Servet Akar Esra Erpek	
14:00-14:15	Sarkoid vaskülit Nedir? Ne Değildir? Olgu Sunumu	Cemal Bes Duygu Sevinç Özgür	
14:15-14:30	Tekrarlayıcı polikondrit seyrinde vaskülit Nedir? Ne değildir? Olgu sunumu	Levent Kılıç Ertuğrul Çağrı Bölek	
14:30-15:00	Kahve arası & Poster turu		
15:00-16:30	**2.OTURUM**		
15:00-15:15	Tek organ vasküliti Nedir? Ne Değildir? Olgu Sunumu	Haner Direskeneli Gizem Sevik	Kenan Aksu, Özay Gököz
15:15-15:30	Kutanöz Lökositoklastik anjiitis Nedir? Ne Değildir? Olgu Sunumu	Tuğçe Arslan Duygu Gülseren	
15:30-15:45	Kutanöz arteritis Nedir? Ne Değildir? Olgu Sunumu	Nazife Şule Yaşar Bilge Burcu Ceren Uludoğan	
15:45-16:00	Hipokomplementemik ürtikeriyal vaskülit Nedir? Ne Değildir? Olgu Sunumu	Sibel Doğan Ecem Bostan	
16:00-16:15	İlaca bağlı ANCA-ilişkili vasküliti nedir? Ne Değildir? Olgu sunumu	Neslihan Yılmaz Cansu Akleylek	
16:15-16:30	Kanser Asosiye Vaskülit Nedir? Ne Değildir? Olgu Sunumu	Gökçe Kenar Artın Tuba Demirci Yıldırım	
16:30-16:45	Kahve arası & Poster turu		
16:45-18:00	**3.OTURUM**		
16:45-17:00	İzole aortitis Nedir? Ne Değildir? Olgu Sunumu	Hamit Küçük Hazan Karadeniz	Fatoş Önen Ayşe Çefle Tuncay Hazırolan
17:00-17:15	Sfiliz İlişkili aortit Nedir? Ne Değildir?	Berivan Bitik	
17:15-17:30	Cogan sendromu Nedir? Ne Değildir? Olgu sunumu	Sevil Kamalı Burak İnce	
17:30-17:50	HCV İlişkili Kryoglobulinemik Vaskülit/Kryogolobulinemik Vaskülit Olgu Örneği	Abdulsamet Erden Bahar Özdemir	
17:50-18:00	Kapanış & Geri bildirimler		

Hacettepe
Vasculitis Workshop, Focus on Less Discussed Vasculitides in Chapel Hill Consensus Conference,
Ankara, Friday, December 16th, 2022

Organizing Committee

Dr. Gizem Ayan
Dr. Emre Bilgin
Prof. Dr. Sibel Doğan Günaydın
Prof. Dr. İhsan Ertenli
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Prof. Dr. Sedat Kiraz
Prof. Dr. Seza Özen

*Sorted alphabetically by surname.

Under the leadership of the Hacettepe Vasculitis Research Center, with the support of the Hacettepe Rheumatology Society and with the participation of those who are interested in vasculitides from all over Turkey, the "Hacettepe Vasculitis Workshop" which has now taken its place in the scientific meeting calendar, was took place successfully in December 2022.

This year, the focus of the workshop was the ''less-discussed vasculitides of Chapel Hill Consensus Conference". All of these vasculitides were discussed in every aspect. Invited speeches were included in this booklet to spread knowledge to the ones who could not attend the workshop.

We want to thank all organizing committee members, speakers, and participants for contributing to this workshop. We also thank specially to Hacettepe Rheumatology Society for the unconditional support that enabled us to conduct this special workshop. We also thank the Editorial Team of Acta Medica for providing us with this space for the booklet.

Emre Bilgin, MD
Guest Associate Editor
Professor Omer Karadag, MD
Guest Editor

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EDITORIAL

Adapting HUVAC Vasculitis Registry to a Country-wide online registry system: Turkish Vasculitis Study Group Prospective Database, TRVaS

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Vasculitides are relatively rare diseases that can affect various organ and tissue systems. Vasculitides can lead to mortality as well as various morbidities. Collaboration with various departments is crucial in the diagnosis, differential diagnosis, and management of the disease. Primary vasculitides, as defined in the Chapel Hill Consensus, are primarily characterized by vasculitides involving large, medium, and small vessels, along with specific subtypes. Additionally, primary vasculitides may exhibit varying patterns of involvement based on different characteristics such as geographic regions, ethnicity, and gender. For example, in the Far East, ANCA-associated vasculitides are frequently seen in the form of microscopic polyangiitis, whereas in our region and Northern Europe, granulomatous polyangiitis is more common. Furthermore, the types and frequencies of vasculitides in childhood and adulthood can differ.

It is evident that, as vasculitides are classified as rare diseases, retrospective data will be limited in determining their epidemiological basics, diagnosis, treatment, and courses. Prospective patient registry systems can provide more comprehensive and descriptive data. In this regard, aiming to increase collaboration among departments in the diagnosis, follow-up, and treatment of vasculitis patients and to establish effective representation and partnerships on national and international platforms through a regular registration system, the Hacettepe University Vasculitis Research Centre (HUVAC) was established in May 2014, and prospective patient registration commenced. The period leading up to the establishment of our center has been discussed in the context of our ANCA-associated vasculitides Workshop volume [1].

HUVAC patient records have provided one of the first significant epidemiological data for our region. The differences in the distribution of vasculitides between childhood and adulthood have been updated as the number of patients has increased. Figure 1 presents the diagnosis and frequency distribution of 2046 adult and 536 pediatric vasculitis patients registered at our center as of June 2023.

Another important point to highlight is the involvement characteristics of the same vasculitides may vary between children and adults. In a study conducted at our center, evaluating 88 adult and 330 pediatric IgA vasculitis cases, spondyloarthritis was only observed in the adult group. At the same time, relapses were more common in pediatric patients. Most pediatric patients did not require additional treatment, whereas more than half of the adults required immunosuppressive therapy. Additionally, this study is the first to examine the use of biological therapy in IgA vasculitis [2].

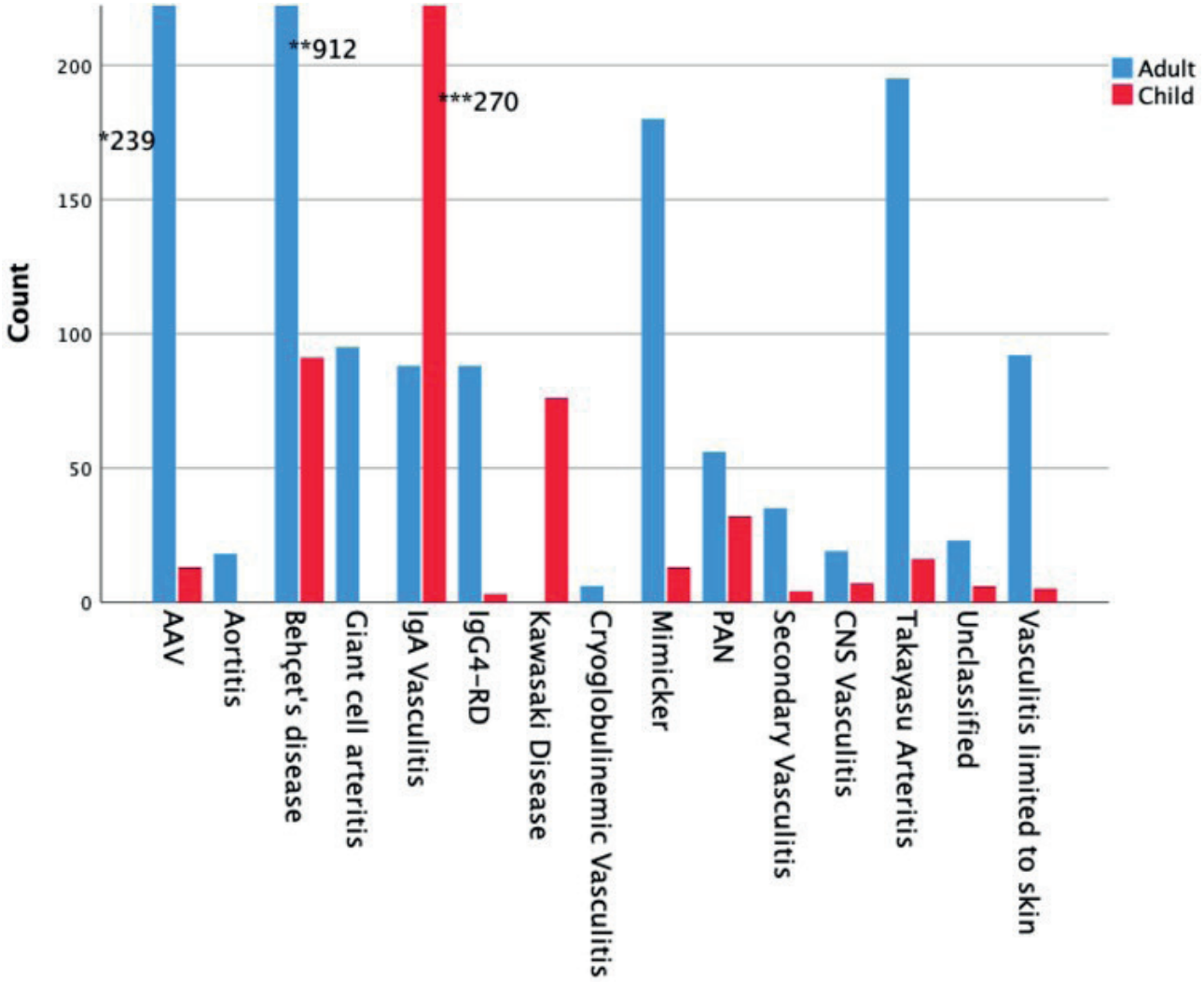

Figure 1. As of June 2023, the distribution of adult and pediatric patients registered in our HUVAC database center.
*n=239 for adult patients with AAV, ** n=912 for adult patients with Behçet's disease, ***n=270 for child patients with IgA vasculitis

In addition to the development of research and projects to track and discuss the current vasculitis literature and to raise awareness about vasculitis, an annual Vasculitis workshop has been organized since 2017. In the COVID era, an online workshop was held in 2020 on ANCA-associated vasculitides. The following year, focusing on Giant Cell Arteritis and Polymyalgia Rheumatica, took place in 2021 in a face-to-face format. Speech summaries and papers from both workshops have been published in the Acta Medica journal [3,4]. Based on the high level of interest and positive feedback received for both workshops, in 2022, a workshop titled 'Chapel Hill Consensus Conference on Less Talked Vasculitides: What Are They? What Are They Not? Real-Life Case Examples' was organized, focusing on vasculitides classified under the 'Rarely Seen Vasculitides' category in the Chapel Hill classification.

Thanks to the increasing prevalence of web-based platforms in our lives during the pandemic, starting from the end of 2020, HUVAC has transitioned to a web-based infrastructure for patient records through a protocol established with Vanderbilt University [5]. While the HUVAC registry continues to evolve, it does have some limitations. Hacettepe University, due to its location and nature, receives referral patients from various regions of Turkey. It is known that the involvement and disease course of the patients who apply for treatment are more severe. Therefore, data obtained from a single center may overlook the milder cases of vasculitides, which represent a heterogeneous patient group.

Therefore, in order to comprehensively and in greater detail investigate Turkey as a country where reflections of Eastern Mediterranean populations

can be observed in the perspective of vasculitis, data of vasculitis patients and mimickers seen in Internal Medicine and Rheumatology clinics in different cities were collected through a web-based RedCap system under the umbrella of the Turkey Vasculitis Study Group (TRVaS) after obtaining necessary approvals and system definitions. The project began with an inventory page for all vasculitis types in 2021, involving six centers. By 2022, TRVaS expanded to include 23 centers, including pediatric rheumatology clinics.

In the current system, patients diagnosed with any vasculitis can be registered in the system. An inventory form is filled out for these patients, which includes demographic information, information related to vasculitis diagnosis (vasculitis type, diagnosis date, affected organ/system, genetic and histopathological examinations, serological markers in some vasculitides, treatments used until the registration date), and data regarding comorbidities. Additionally, there is a disease-specific form for ANCA-associated vasculitides.

In addition to routine patient records, project proposals created by researchers are evaluated by the steering committee. Forms specific to approved projects are generated, and centers are invited for data entry.

In last two years, several disease-specific and disease-based project forms were added to the TRVaS database. Herein, we will provide the novelties in the TRVaS database.

1. AAV disease-specific form

There is a form specific to AAV on the TRVaS database, which was created to record the basic characteristics and information of patients diagnosed with ANCA-associated vasculitis. This form is open for data entry of all centers. In this form, data is collected under the following headings: demographic characteristics such as age, gender, and date of birth; anthropometric measurements; habits such as smoking, alcohol; AAV-specific variables such as AAV type, date of diagnosis, date of symptom onset, antibody status, organ involvement at presentation and during the course, activity and damage indices, immunosuppressives used in remission and maintenance, and relapse status; accompanying comorbidities. It is planned to collect longitudinal data by introducing the visit form by the end of this year.

2. AAV Project forms

2.1. External validation of DCVAS ANCA vasculitis criteria

A separate form was created for the external validation of the classification criteria developed by the DCVAS group specifically for ANCA-associated vasculitides. Preliminary data from this project were presented at the 2023 EULAR Congress. In this study, which included a total of 820 AAV, 47 PAN, and 76 IgA vasculitis patients, using 2022 ACR/EULAR Classification Criteria, improved sensitivity and specificity for GPA and sensitivity for EGPA were observed. Additionally, half of the unclassified AAV patients could be classified as either GPA or MPA. These criteria functioned well for the discrimination of patients with AAV from other small/medium vessel vasculitides such as PAN and IgA vasculitis. In total, over 80% of the patients with AAV were accordingly classified parallel to the clinical diagnosis in each GPA/EGPA/MPA group [6]. The final data of the study are in the publication phase.

2.2. Metabolic Syndrome among patients with AAV

This form was opened within the scope of the "Multicentre Study of the Prevalence of Metabolic Syndrome in Patients with ANCA-Associated Vasculitis (AAV)". Many recent studies have emphasized the increased cardiovascular disease (CVD) risk in AAV patients [7,8]. While most AAV patients develop hypertension, diabetes mellitus and dyslipidemia, the mechanisms of accelerated atherosclerosis in AAV patients are not fully understood. Vascular inflammation, arterial wall injury and immunosuppressive drugs may contribute to the acceleration of atherosclerosis [9]. Metabolic syndrome (Met S) is a cluster of CV risk factors, including insulin resistance syndrome, obesity, hyperglycemia,

hypertension, hypertriglyceridemia and low HDL, and is associated with an increased risk for CVD and type 2 diabetes mellitus [10]. To date, there are limited data on Met S and related factors in patients diagnosed with AAV [11]. In a study conducted at Marmara University, 37 patients diagnosed with AAV were investigated and it was observed that the frequency of metabolic syndrome increased in patients with AAV [12]. Based on this study, it is planned to initiate a study involving the Vasculitis Centres that have come together within the Turkish Vasculitis Database (TRVaS), which aims to evaluate AAV patients in Turkey in a multicentre manner. With this multicentre study including a larger number of patients, it is aimed to investigate the frequency of Met S in AAV patients and to examine the link between clinical and laboratory parameters of AAV and Met S to reveal the effect of Met S in the etiology of CVD occurring in AAV patients.

2.3. Identification of Osteoporosis in AAV

It has been shown that the frequency of osteoporosis and osteopenia increases in AAV patients [13]. Chronic inflammation is present in AAV patients and pulse steroid treatment can be used in induction and followed by maintenance steroid treatment [14-16]. The AAV-osteoporosis association may be explained using immunosuppressive therapies, especially glucocorticoids, or directly by inflammation or impaired renal function [17]. It is predicted that the development of osteoporosis may be accelerated by various factors such as these in AAV patients. In our country, a small-scale study examining FRAX score in AAV patients was conducted and it was shown that the risk of fracture increased compared to healthy controls [18]. This study was designed as a retrospective study on adult AAV patients in TRVaS to determine the prevalence and predictive factors of osteoporosis in AAV patients in Turkey. Early data will be discussed at the National Rheumatology Congress in 2023.

2.4. Venous thromboembolism in AAV

There are reports suggesting that venous thromboembolism (VTE) may be a disease involvement or AAV may be a predisposing factor for VTE [19-26]. In the RAVE study conducted in 2019, VTE was detected in 16/197 patients showing, presence of pulmonary hemorrhage, PR3-ANCA positivity, cardiac involvement and presence of erythrocyte silica in urine as risk factors for VTE in AAV patients in multivariate analysis [24]. In another study, the incidence of VTE was calculated as 2.4/100 patient-years [25]. They reported that the incidence of VTE was highest in the first 3 months following diagnosis (20.4/100 patient-years, 95% CI 11.5-29.4), 8.9/100 patient-years (95% CI 0.2-17.6) in 4-6 months, and 1.5/100 (95% CI 0.0-3.5) in 7-12 months. In this study, disease activity and age were reported to be risk factors for AAV-related VTE [25]. In this project, aim is to determine the frequency of all VTE events and subgroups in the cohort of Turkish patients with AAV and to determine the factors associated with VTE development, if any. We also planned to investigate whether there is a difference in AAV subgroups.

2.5. The translation of the AAV-PRO Patient-Reported Outcome Measure into Turkish and its validity and reliability in Turkish translation

In 2018, the AAV- Patient-Reported Outcome (PRO) measures questionnaire, developed by the University of Oxford, which assesses the quality of life of patients with ANCA-associated vasculitis in six subdomains, was translated into Turkish. The Turkish version of this questionnaire can be accessed through this link [27]. Hacettepe University, Gazi University, and İzmir Katip Çelebi University, as data providers for TRVaS, are collaborating on a validity and reliability study of the Turkish version of the AAV-PRO questionnaire. The preliminary data of the study were presented at the 2022 National Rheumatology Congress and the 20th International Vasculitis and ANCA Workshop [28].

3. IgG4 related disease form

In 2022, a form was created for IgG4-related disease, recording disease-related and treatment-related characteristics. This form focuses on both the classification criteria for IgG4-related disease and the IgG4-related Disease Responder Index, and relevant variables are recorded. The initial data for this data form, which includes both adult and pediatric patients, will be discussed at the 2023 National Rheumatology Congress.

4. IgA vasculitis disease specific form

IgA vasculitis (previously known as Henoch Schönlein purpura) is the most common primary systemic vasculitis in childhood. The estimated incidence is 3-26.7 per 100,000 cases [29-31]. It is a small vessel vasculitis characterized by IgA immune deposits in the skin, gastrointestinal tract, and kidney and arthritis/arthralgia. Early recognition of the disease and initiation of correct and effective treatment is important. A study to be conducted in our country on the evaluation of patients diagnosed with IgA vasculitis in childhood and adults (when the patients were diagnosed, clinical course, laboratory data, biopsies if available, presence of comorbidities, and treatment) will increase the knowledge of physicians about the general characteristics of the disease and its distribution according to age, contribute to the determination of the prognostic factors of the disease, and shape the algorithm to be followed in the follow-up of patients. For this purpose, the study group is still working on IgA vasculitis form and planning to open the page by the end of this year.

a. Future Prospects

TRVAS has been invited to join FAIRVASC, a research project of the European Vasculitis Society (EUVAS) and the RITA European Reference Network. Major national registries include the Irish Rare Kidney Disease Registry, the UKIVAS Registry, the French Vasculitis Study Group Registry, the Czech Vasculitis Registry, the Polish Vasculitis Registry POLVAS, the new German/Austrian/Swiss GEVAS Registry, and the Swedish Skåne Vasculitis Inception Cohort, all partners in FAIRVASC. FAIRVASC uses the same data coding system as TRVas and after a bureaucratic procedure TRVaS is soon planned to join FAIRVASC. More information can be found on this website: https://fairvasc.eu.

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INVITED REVIEWS

What is isolated / idiopathic / non-syndromic aortitis? What is not?

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Definition: Aortitis is a non-specific inflammation that affects any of the aorta wall layers, regardless of the underlying etiology [1]. The causes of aortitis are evaluated under two main headings infectious and non-infectious causes. The main infectious causes include; salmonella, staphylococcus aureus, syphilis, hepatitis B and C, HIV, histoplasmosis, and tuberculosis. The main non-infectious causes include; large vessel vasculitis such as giant cell arteritis (GCA) and Takayasu arteritis (TA), sarcoidosis, IgG4-RD, Behçet's disease, Cogan syndrome, Erdheim-Chester disease, connective tissue disease, and idiopathic aortitis (IA) [2]. Idiopathic aortitis, which is a diagnosis of exclusion, is defined by an aortic wall thickening >2 mm on computed tomography/magnetic resonance (CT/MR) and/or aortic aneurysm associated with an unexplained inflammatory syndrome (C-reactive protein (CRP) or fibrinogen elevation).

Clinical Features: Although idiopathic aortitis clinic is mostly asymptomatic, nonspecific constitutional symptoms such as fever, malaise, weight loss, myalgia, resistant blunt back and chest pain, abdominal pain, vascular insufficiency, and progressive cough may occur.

Diagnosis (Radiology & Histopathology): The initial evaluation of a patient with all aortitis requires rapid differential diagnosis of the infectious etiology because of its rapid progression, complications, and high mortality [3]. Radiological and nuclear imaging (CT/MR and positron emission tomography scan) evaluated along with clinical, histopathologically, and laboratory findings increase diagnostic accuracy. Apart from diagnostic evaluation, radiological and nuclear imaging is also helpful in measuring disease activity, treatment plans, and post-treatment follow-up [4]. Vessel aneurysm, ectasia, wall thickening, dissection, stenosis, and thrombosis are the most common radiological findings. Histopathologically, aortitis classification is divided into 4 groups;

1. **Granulomatous/giant cell pattern of inflammation;** Idiopathic aortitis, GCA, TA, rheumatoid vasculitis, sarcoidosis, granulomatous polyangiitis, a mycobacterial and fungal infection.
2. **The lymphoplasmacytic pattern of inflammation;** (lymphocytes and plasma cells without a granulomatous/giant cell component); IgG4-related disease, syphilis, ankylosing spondylitis, systemic lupus erythematosus.
3. **Suppurative pattern of inflammation;** Gram positive cocci, pseudomonas, salmonella.
4. **Mixed inflammatory pattern;** (lymphocytes, plasma cells, macrophages, neutrophils, mast cells, and eosinophils); Behçet disease, Cogan syndrome, relapsing polychondritis.

Differential diagnosis:

– **Takayasu arteritis;** luminal narrowing or occlusion, discrepant blood pressure between arms, arterial bruit, limb claudication, carotidynia, absent or diminished peripheral pulses, hypertension.

- **Temporal arteritis;** Isolated aortitis demonstrates a granulomatous/giant cell pattern histopathologically. It cannot be distinguished histopathologically. Headache, abrupt onset of visual disturbances, jaw claudication, limb claudication, and temporal artery abnormalities such as tenderness to palpation.
- **Relapsing polychondritis;** inflammation in cartilaginous structures and other tissues throughout the body, particularly the ears, nose, eyes, joints, and respiratory tract.
- **Erdheim -Chester disease;** multifocal sclerotic lesions of the long bones demonstrating sheets of foamy histiocytes on biopsy.
- **Cogan syndrome;** clinical hallmarks are interstitial keratitis and vestibulo auditory dysfunction.
- **Sarcoidosis;** bilateral hilar adenopathy, pulmonary reticular opacities, skin, joint, and/or eye lesions, ACE↑, urine calcium↑.
- **IgG4-related disease;** tumor-like swelling of involved organs.

CASE PRESENTATION

A 51-year-old female patient who had a history of hypertension, Hashimoto's disease, and migraine presented to our clinic in 2017 with non-productive progressive cough, myalgia, subfebrile fever, back and chest pain, bilateral proximal arm pain for the last one year. There were no remarkable findings on physical examination. Blood tests revealed elevated CRP (26.3 mg/dl, ULN>5) and erythrocyte sedimentation rate 78 mm/h (ULN>20 mm/h), leukocyte (6624/mm3), neutrophil (2500/mm^3) with negative serology of RF (IU/ml), CCP (U/ml), ANA .

Since the patient's symptoms and acute phase reactant elevation continued for 1 year, malignancy screening was initially performed. A peripheral blood smear, mammography screening, and the fecal occult blood test were negative. Thorax CT; A few parenchymal nodules, the largest of which is 6 mm, in ACs, soft tissue increase measuring 1 cm in the thickest part around the ascending aorta. The soft tissue augmentation begins at the root of the aorta just superior to the level of the valsalva and extends superiorly along the ascending aorta (aortitis?) (Figure 1).

Infectious tests were requested first because of an aortitis report on thorax CT. HBV, HCV, anti-HIV, Toxo IgM, anti-rubella IgM, CMV IgM VDRL, Brucella, Grubal widal , IGRA results were all negative. Echocardiography was normal (ejection fraction 65%, pulmonary artery pressure normal) and no pathology was detected in pelvic X-ray. The patient was diagnosed with non-infective isolated aortitis and prednisolone (20 mg/day) plus oral methotrexate (10 mg/week)were started. One month later, both clinical improvement and normalization at acute phase levels were seen. Prednisolone was gradually tapered and completely discontinued at 6 months. However, radiological and clinical progression was detected first year MR imaging (wall thickening in isolated ascending aorta and increased anteroposterior diameter of the ascending aorta (dilatation << progression). SC certolizumab (200 mg /ml/ 2 weeks) treatment was started due to disease progression. Due to itching and clinical unresponsiveness after certolizumab,

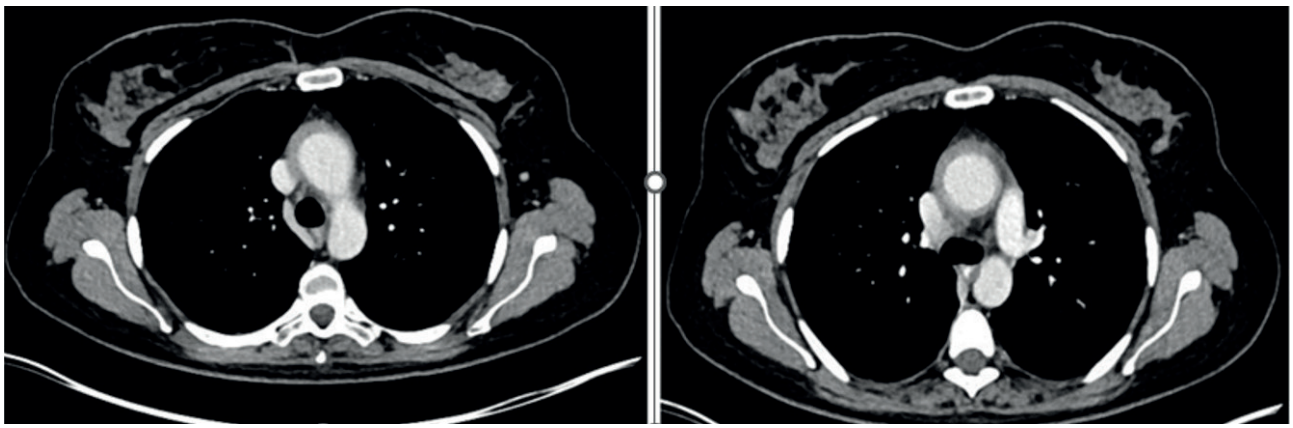

Figure 1. Axial CT scans acquired during the venous phase show concentric wall thickening of the aorta characterized by an internal hypoattenuating ring.

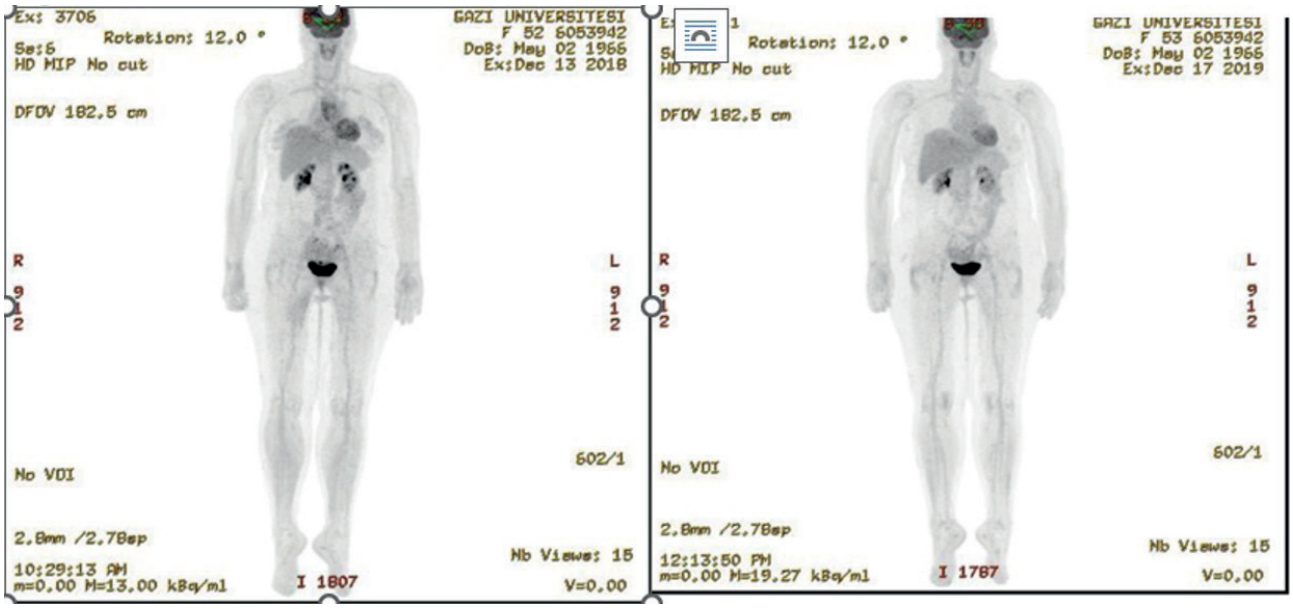

Figure 2. Increased FDG uptake in the aorta and disappearance of aortic involvement (2022) after tocilizumab treatment in 2019.

it was switched to SC tocilizumab (162 mg/week) treatment. After the SC tocilizumab treatment, she has no clinical complaints or radiological regression for about three years (Figure 2).

Key messages

- The initial evaluation of a patient with aortitis requires rapid differential diagnosis of the infectious etiology because of its rapid progression, complications, and high mortality.
- Location of aortic involvement; ascending, arc us, and descending aorta, suprarenal abdominal aorta, subrenal abdominal aorta, or entire aorta. Tobacco use, older age, connective tissue disease, diabetes mellitus, heart valve disorder, and family history of aortic aneurysm are among the risk factors.
- To prevent the development of life-threatening complications of IA, corticosteroids should be initiated.
- Apart from steroids, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNF inhibitors (in refractory cases) are preferred.
- In medical treatment failure or severe aortic regurgitation , surgical procedures may need to apply such as aneurysmectomy, arterial reconstruction or aortic valve operation.
- The 5-year event-free survival for patients with IA is 38%.

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INVITED REVIEWS

Drug-associated ANCA-associated vasculitis: Overview based on Chapel Hill Conference Consensus 2012 and a case report

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Definition

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of small vessel vasculitides characterized by necrotizing inflammation with few or no immune complexes and classifed as primary or secondary based on underlying causes (various drugs, infections or malignancy vs). Drug-associated AAV is the one of most common cause of secondary form and characterized by use of spesific drugs [anti-thyroid drugs (propylthiouracil, carbimazole, methimazole), antibiotics (cefotaxime, minocycline, nitrofurantoin), TNF-inhibitors, sulfasalazine, allopurinol, D-penicillamine, isoniazid] that strongly related to vasculary inflammation while other etiologies are excluded [1]. The 2012 International Chapel Hill Consensus Conference classified drug-associated AAV as vasculitis associated with probable etiology [2].

Clinical Features

Drug-associated AAV presents with variable clinical findings and often mimics primary systemic vasculitis with manifestation of the cutaneous, renal and/or pulmonary involvement. Although it is difficult to distinguish of the drug-associated AAV from primary AAV by clinical and laboratory markers, some differences have been reported such as having a better prognosis, less severe disease, and less renal and major organ involvement [3].

Anti-thyroid drugs, especially propylthiouracil, is the most common cause of drug-associated AAV and considering the epidemyology of hyperthroidism, usually effect young and female population with mild symptoms [4]. Skin involvoment is the most common manifestations with petechiae, purpura, ulcer and necrosis. Renal involvement may be seen with mild severity.Pulmonary, gastrointestinal, nervous system involvement and constitutional symptoms are less frequent in drug-associated AAV compared to primary vasculitis [5,6].

There are no unique clinicopathological or laboratory markers that can distinguish drug-associated AAV from primary AAV. Similar to primary AAV, anemia, urinary abnormalities, increased creatinineurinary protein, and acute phase reactants levels may be present. Most patients with drug-associated AAV have a positive MPO-ANCA rather than PR3-ANCA. In addition ANCAs may recognize many target neutrophil antigens in this groups and both MPO-ANCA and PR3-ANCA positivity could be seen in the same patient. The other antibodies such as ANA, anti histone, anticardiolipine and anti b2-glycoprotein could be detected in drug-associated AAV and the presence of these autoantibodies can help differantiate from primary AAV [3].

Diagnosis

The diagnosis of drug-induced vasculitis is complicated due to variable clinical presentations and similar clinical and laboratory features with primary AAV. The pathological assesment such as tissue biopsy from skin lesions, renal and lung usually provide a diagnosis of vascular inflammation

to exclude other etiologies. Currently, there is no clear definition or a diagnostic criteria for drug-induced AAV. However, some papers reported some criteria that can be used for diagnosis. In an article, it is recommended that drug-induced AAV can be considered in the presence of the following conditions, after the other etiologies (infections, malignancies and other types of vasculitis) are excluded: (a) meeting the 2012 Chapel Hill Consensus Conference definition for AAV (b) positive serum ANCA (c) the clinical symptoms of vasculitis are induced with using the suspicious drug and regressed with discontinuation [7].

The main and most important principle of the treatment is withdrawal of the drug though to be responsible for vasculitis. In most cases, improvement is observed after discontinuation of the drug [1]. Immunosuppressive drugs should be reserved only severe and sustained clinical manifestations.

CASE PRESENTATION

A 63-year-old male patient was admitted to the rheumatology outpatient clinic in March 2017 due to the spread of rash around his ankles and calfs, which started 20 days ago. He had weakness, fatigue, and pain in his ankles and wrists for the last 3 days. He denied any recent infection, fever, cough, dyspnea, sinusitis symptoms, neuropathic complaints, and abdominal pain. He had a history of diabetes mellitus, hypothyroidism, hyperlipidemia, hypertension, coronary artery disease and atrial fibrillation. He was being treated with metformin 850mg/day, gliclazide 60 mg/day, propylthiouracil 150 mg/day, acetylsalicylic acid 150 mg/day, atorvastatin 20 mg/day, metoprolol 50 mg/day and warfarine 5 mg. In admission to the hospital, diffuse hemorrhagic bullae and erosions, necrotic ulcerations, and palpable purpura on bilateral lower extremities were seen. In laboratory evaluation, leukocytosis (13200 mm^3/uL), anemia (10.2 g/dl), thrombocytosis (535000 mm^3/uL), high level of creatinine (4.2 mg/dl) and acute phase reactants [CRP (38 mg/L), sedimentation (63 mm/h)], abnormality of coagulation test (INR:13) and hematuria (RBC 3 positive) were found. Echocardiography, chest X-ray, thoracic and abdominal CT scans were unremarkable.

In his follow-up, he suffered bloody stool. Duodenal ulcer was found in endoscopic examination. Renal and skin biopsies were planned, but renal biopsy could not be performed due to warfarine overdose

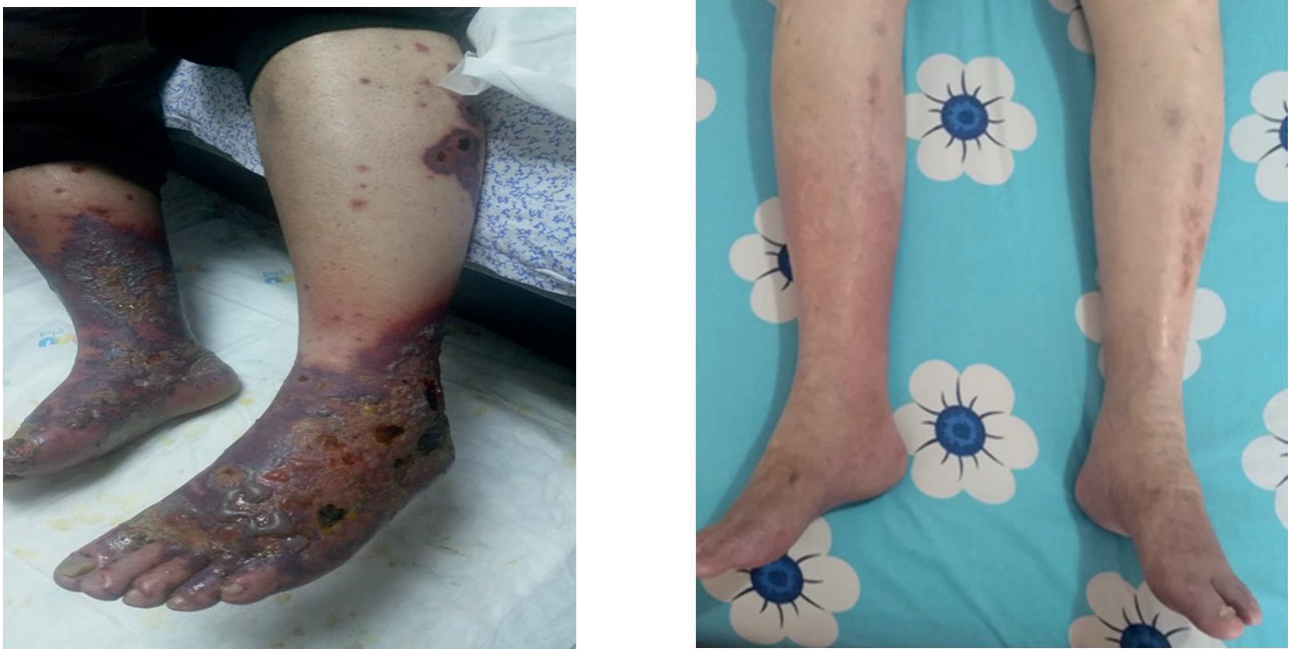

Figure 1. Before treatment (a) and after treatment (b).

and patient preference. Warfarin, statin, and PTU were discontinued because of the possibility of drug-related eruptions. His skin biopsy revealed leukocytoclastic vasculitis. Further evaluation revealed p-ANCA and anti MPO ELISA positivity. The patient was evaluated as "PTU-associated AAV" thus 1 mg/kg/day prednisone treatment was started. On the 7th day of treatment, creatinine (1mg/dl) and CRP (5 mg/l) levels were found normal and urinalysis was unremarkable. In the follow-up, the skin findings, joint complaints and constitutional symptoms improved. While the steroid dose was decreased, the lesions did not relapsed and no additional systemic involvement developed.

Key messages

- Propylthiouracil (PTU) is a commonly used antithyroid medication, can induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Compared with primary AAV, PTU-induced vasculitis generally has a mild disease severity with good prognosis.
- A standard treatment protocol is not clear for drug-induced AAV and should be based on disease activity and severity. While for patients who had mild symptoms, without organ involvement, cessation of drug might be sufficient to induce disease remission while active management is reserved for patients with more severe conditions.

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INVITED REVIEWS

Cogan's syndrome

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INTRODUCTION

Cogan's syndrome (CS) is a rare inflammatory disorder that was first described by David Cogan in 1945 [1]. It is distinguished by the presence of ocular inflammation (non-syphilitic interstitial keratitis) and audiovestibular dysfunction occurring within a few months. The incidence of CS is unknown. It mostly affects young adults (peak incidence: 20-30 years); there is no known sex or racial predominance [2]. CS can also cause systemic vasculitis, which was included in the "variable vessel vasculitis" category in Chapel Hill Consensus Criteria.

Definition

CS vasculitis is defined as vasculitis occurring in patients with CS, characterized by interstitial keratitis, uveitis, episcleritis, and inner ear disease. Vasculitic manifestations may include arteritis (affecting small, medium, or large arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis [3].

Clinical Features

The most frequent ocular feature of CS is non-syphilitic interstitial keratitis. Iridocyclitis, conjunctivitis, episcleritis, and retinal scleritis are other common ocular findings of CS. The ear symptoms of CS are characterized by attacks consisting of vertigo, ataxia, nausea, vomiting, and tinnitus, leading to sensorineural hearing loss (SNHL). Symptoms such as fever, weight loss, arthralgia, myalgia, lymphadenopathy, hepatosplenomegaly, and abdominal pain may be seen in 50-80% of patients complicated with systemic vasculitis.

Aortitis is the most frequent vascular involvement in CS, although the size of vessels can be affected. Aortic insufficiency related to aortitis is not a frequent (10%) complication of CS. Limb claudication due to stenotic or occlusive lesions may also be seen in CS with large vessel vasculitis [4,5].

Diagnosis

Characteristic involvement of both eyes and inner ear is essential for the definite diagnosis of CS. Infections, malignancies, and other primary or secondary vasculitides should be excluded, especially in suspected cases. There are no diagnostic autoantibodies or specific radiologic findings for CS vasculitis. Although the ascending aorta is mostly involved in cross-sectional imaging, the entire aorta can be affected, and aneurysmal dilatation may develop.

Differential diagnosis

The different disease spectrums that cause oculovestibular symptoms are included in the differential diagnosis of CS. Sarcoidosis, Voyt-Koyanagi-Harada syndrome, Susac Syndrome, and infections including syphilis, tuberculosis, Chlamydia spp., Herpesviridae, Parvovirus b19, and Lyme disease can be counted among these diseases. Aortitis seen in Takayasu arteritis (TA)

is indistinguishable from CS aortitis, and TA may also rarely cause autoimmune membranous labyrinthitis, uveitis, and scleritis. Granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis may also cause Meniere-like symptoms and sensorineural hearing loss similar to CS. Therefore, these conditions should also be considered in differential diagnosis.

Management

Topical glucocorticoids are the first options for mild ocular disease, although extensive ocular and ear disease usually requires oral glucocorticoids or immunosuppressive therapy. An open-label study of etanercept for immune-mediated cochleovestibular disease did not show significant benefit [6].

There are no controlled trials on the treatment of systemic findings of CS. High-dose glucocorticoids are the initial treatment for systemic vasculitis. csDMARDs such as methotrexate, azathioprine, and cyclosporin A are usually suggested as concomitant therapy. TNF inhibitors, JAK inhibitors, and rituximab may be used in resistant cases [7].

Prognosis

Frequent relapses of eye and inner ear disease may occur during the disease course. Ocular outcomes of CS are usually favorable. Sensorineural hearing loss is mostly irreversible. Nevertheless, improvement with early use of immunosuppressive drugs is also reported [8]. There is insufficient data on the prognosis of CS patients with systemic vasculitis, as a rare vasculitic condition.

CASE PRESENTATION

Twenty-year-old male with a history of pulse steroid treatment due to sudden sensorineural hearing loss in both ears applied to our clinic with blurred vision and left ankle pain ten years ago. Physical examination revealed asymmetric oligoarthritis and redness in both eyes. Eye examination showed nodular scleritis. Cardiovascular examination and thorax MRI angiograph were normal. High-dose methylprednisolone (MP) and methotrexate (MTX) 15 mg weekly were prescribed with the diagnosis of Cogan Syndrome. MTX switched to azathioprine six months later for the persistent disease activity, but no improvement was observed. After the first year of follow-up, the patient was hospitalized with tachycardia and chest pain. He had high pitched aortic regurgitation murmur in physical examination. PET-CT revealed aortitis with involvement of the aortic valve and posterior ascending aorta (SUVmax: 5.2). Rheumatoid factor, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-phospholipid syndrome screening, and VDRL tests were negative. High-dose corticosteroid and TNF-alpha inhibitor treatment (Infliximab 5 mg/kg) were started for remission induction. The patient was admitted with fever, palpitation, dyspnea, necrotic ulcer on the sole, acrocyanosis, and splinter hemorrhages in the third month of follow-up. Echocardiography revealed severe (+3) aortic regurgitation. There were no relevant pathogens on repeated blood cultures. The patient was diagnosed with resistant systemic vasculitis associated with CS and treated with pulse MP for 3 days and cyclophosphamide 500 mg every two weeks for 3 months. Rituximab (RTX) (1 g, 6-12 monthly) was commenced as the maintenance therapy. Remission could be achieved for 5 years of follow-up.

Key messages

CS vasculitis has to be kept in mind in patients with systemic vasculitis who had a current or previous history of inflammatory inner ear disease resulting in hearing loss and inflammatory ocular disease within a certain time period.

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INVITED REVIEWS

What is lupus vasculitis? A case with diffuse alveolar hemorrhage

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Definition and Classification: Systemic lupus erythematosus (SLE) is a multifactorial systemic autoimmune disease caused by a loss of tolerance to self-antigens, mainly nuclear antigens (deoxyribonucleic acid, ribonucleic acid, and nuclear proteins). It is characterized by aberrant T- and B-cell responses, autoantibody production, and immune complex deposition in tissues with complement activation, inflammation, and irreversible organ damage [1]. SLE can affect any organ system as well as vessels, resulting in a wide range of clinical presentations. Lupus vasculitis prevalence fluctuates between 11 and 35.9%, even though large studies and cohorts addressing specifically vasculitis in lupus are very few [2]. It predominantly involves small vessels; medium-sized vessels can also be affected, and large vessel involvement is very rare [3,4]. It is difficult and controversial to completely separate the organ involvement of lupus from the vasculitis of lupus. For example, diffuse proliferative lupus nephritis and central nervous system involvement due to lupus are considered as vasculitic involvements by some authors. Episodes of vasculitis often occur during a "lupus flare," with constitutional symptoms such as fever, fatigue, and weight loss; a higher prevalence of livedo reticularis, anemia, elevated erythrocyte sedimentation rate, and anti-La/SS-B has been reported as well. Longer disease duration and younger age at the onset of the disease have been reported as risk factors for the development of LV [5,6]. In most cases, other manifestations of lupus precede the onset of vasculitis; it is the initial presentation in approximately 20% of the cases [7]. Vasculitides secondary to SLE are classified under the 'vasculitis associated with systemic disease' category according to the revised International Chapel Hill Consensus Conference (CHCC) nomenclature [8].

Clinical Features and Diagnosis: In ninety percent of SLE cases, vasculitis affects the skin. Internal organ involvement occurs in about 6–18% of cases of LV, according to different series. Even though it is not frequent, visceral involvement is associated with increased mortality [9]. The kidneys, gastrointestinal tract, nervous system (central and peripheral), retina, lungs, heart, and aorta can be involved with lower frequency [4,10-12].

Cutaneous Vasculitis: Cutaneous vasculitis is the most frequent type of vasculitis among patients with SLE. It is reported in up to 19–28% of patients with SLE [13,14]. High levels of anti-Ro and antiphospholipid antibodies (aPL) and positivity for cryoglobulins are associated with a major risk of developing cutaneous LV [5,15,16]. The clinical presentation of cutaneous LV is heterogeneous and includes palpable purpura, petechiae, papulonodular lesions, urticaria like, or bullous lesions of the extremities, livedo reticularis, cutaneous infarction, erythematous plaques or macules, erythema with necrosis, panniculitis, splinter hemorrhages, and superficial ulcerations [17]. Small vessels, principally post-capillary venules, are involved in most cases. Medium-vessel vasculitis is less frequent and appears as subcutaneous nodules or ischemic ulcers [4]. Myositis and hematological manifestations such as anemia, Coombs' positivity, leucopenia, anti-Smith, and anti-RNP (ribonucleoprotein) may predict cutaneous vasculitis developments [18]. In

two large cohort studies in patients with vasculitis and SLE, the most frequent type of vasculitis was reported as leukocytoclastic vasculitis (60%), followed by cryoglobulinemic vasculitis (25–30%) and urticarial vasculitis (7%) [5,6].

Nervous System Vasculitis: Nervous system involvement in SLE patients can be very heterogeneous, but it is definitively not uncommon; neuropsychiatric manifestations (NPs) occur in between 37 % and 90 % of patients with lupus [19]. It can also be seen as peripheral or central nervous system vasculitis (CNS). It is mostly seen in SLE patients with high disease activity. It is frequently seen in the form of non-inflammatory microangiopathy characterized by microinfarction and thrombosis in the brain, and rarely as inflammatory CNS vasculitis [20,21]. At the peripheral level, the most common clinical manifestation is the mononeuritis multiplex; histologically characterized by chronic axonal degeneration, necrotizing, or occlusive vasculitis of the vasa nervorum and demyelination. At the central level; cognitive dysfunction, demyelinating syndrome, cerebrovascular disease, and seizure are the most common clinical manifestations [22,23]. The diagnosis of central nervous vasculitis is a challenge for clinicians. A brain biopsy is the gold standard for the diagnosis, although it is a highly invasive procedure with a limited sensitivity due to the segmental nature of the vascular lesions. The combination of imaging (most often contrast-enhanced cranial magnetic resonance imaging (MRI), angiographic imaging) and other diagnostic tools help us in making an early diagnosis without biopsy [24].

Gastrointestinal Vasculitis: Gastrointestinal involvement is rare but severe as it often causes ischemia and potentially intestinal necrosis, perforation and bleeding. Lupus enteritis-lupus mesenteric vasculitis was reported in 0.2-14.2% of patients [25]. As a result of superior mesenteric artery (SMA) involvement with a rate of 80-85%, the ileum and jejunum are frequently affected. The colon, especially the rectum, is rarely affected. The gastrointestinal vasculitis most often presents with abdominal pain. The main diagnostic test is abdominal computed tomographic (CT) angiography; intestinal wall edema, target sign, and intestinal dilatation are expected images. Relapse has been reported in up to 32% of patients [26]. Liver and pancreatic vasculitis have also been reported in 18-20% of autopsy cases [27].

Renal Vasculitis: Lupus nephritis (LN) is one of SLE's most common and severe manifestations. The renal histopathological lesions are closely associated with different clinical characteristics, therapeutic responses, and outcomes in LN patients [28], and can present as glomerular, tubulo-interstitial, and micro-vascular lesions. Renal microvascular lesions are common in LN and are becoming increasingly recognized as a hallmark of the disease. In addition to glomerulonephritis, there is accumulating evidence showing that renal vascular lesions can adversely affect long-term renal outcomes and might play an important role in the therapeutic strategy choice [29,30]. A diffuse proliferative glomerulonephritis is considered by some authors as the most frequent form of renal vasculitis involving glomerular capillaries. However, the general agreement is that these lesions should be classified as proliferative lupus glomerulonephritis [31]. Basically, 5 renal microvascular lesion types have been identified; these are (a) uncomplicated vascular immune complex deposits (ICD), (b) arteriosclerosis (AS), (c) non-inflammatory necrotizing vasculopathy (NNV), (d) thrombotic microangiopathy (TMA) and (e) true renal vasculitis (TV) [31].

Retinal Vasculitis: Retinal vasculitis is very rare and has only been published as case reports. Although the exact pathogenesis is unclear, it is thought that immune complex deposition, complement activation, and aPL play a role [32]. Typically, the precapillary superficial arterial vasculature is involved [33]. Retinal vasculitis can present as asymptomatic or with painless blurred vision, decreased vision, or permanent visual loss. A funduscopic examination reveals retinal vessel sheathing, cotton wool spots, retinal hemorrhage, and vascular occlusion [34]. Retinal imaging, including fluorescein angiography and optical coherence tomography, can be helpful in the identification and characterization of retinal vasculitis [34,35].

Coronary Vasculitis: Coronary vasculitis is very rare and unlike other types of vasculitis, it was found to be weakly correlated with disease activity [36]. The diagnosis is usually made by serial coronary angiographies that disclose arterial aneurysms, tapered stenoses, and/or rapidly developing arterial occlusions [37].

Pulmonary Vasculitis: The most common clinical manifestation of lupus pulmonary vasculitis is diffuse alveolar hemorrhage (DAH) due to the erythrocyte extravasation into the alveolar spaces as a result of the widespread damage of the pulmonary vessels with disruption of the alveolar-capillary basement membrane [38]. The combination of dyspnea, hemoptysis, decrease in hemoglobin levels, decreased diffusing capacity for carbon monoxide, and pulmonary interstitial or alveolar infiltrates should warn about the possibility of DAH. This is particularly be considered for patients with active SLE [39]. A chest radiography, CT, bronchoscopy, and bronchial lavage can be useful in the diagnosis. Histopathologically, capillaritis and mononuclear cell infiltrates, alveolar necrosis, and immune complex deposits of IgG and C3 can be found [40]. These changes are similar to lupus microangiopathy of the kidneys [36].

Lupus Vasculitis and Antiphospholipid Syndrome: Often LV and APS coexist (especially with retinal, renal vasculitis and alveolar hemorrhage). The concomitant presence of vasculitis and APS is associated with a poor outcome [41,42].

Lupus Aortitis: Until now only 5 cases of lupus aortitis were reported. It can be seen at any age, the ascending aorta is most frequently involved in the form of wall thickening. The most striking finding is abnormal CRP elevation. Therefore, it was suggested to investigate aortitis in SLE patients with abnormal CRP elevation and could not be explained by other reasons [43].

Management: Therapeutic randomized trials to help the clinicians in LV are lacking, therefore information is mainly based on case reports and small case series.. Treatment modalities vary depending upon the presentation and severity of organ involvement. LV can be fulminant and life-threatening, thus prompt treatment is essential [44]. Cutaneous vasculitis often responds to antimalarials (hydroxychloroquine), dapsone or thalidomide. Short courses of corticosteroids may be used if a rapid response is desired [45]. For visceral involvement, intravenous methylprednisolone pulse therapy or high-dose prednisone have been reported to be useful [46], and has been administered along with other immunosuppressants, mainly cyclophosphamide or rituximab as induction therapy, and varying regimens of azathioprine, mycophenolate mofetil, and hydroxychloroquine used for maintenance [47-49].

CASE PRESENTATION

A 33-year-old female patient was being followed up in the nephrology inpatient service because of acute renal failure requiring dialysis. She was admitted to the hospital with newly developed edema, shortness of breath and fatigue. Laboratory tests were performed and revealed a creatinine value of 5.2 mg/dl, BUN of 144 mg/dl, pleural-pericardial fluid and pulmonary edema were reported in thorax computed tomography, on echocardiography showed an ejection fraction of 65% and pericardial fluid without compression. Two years ago the patient was diagnosed as SLE due to arthritis, hematological involvement, antinuclear antibody (ANA) and dsDNA positivity as well. She was put on hydroxychloroquine of 200 mg/day, azathioprine of 100, and methylprednisolone treatment. The patient was consulted to the rheumatology clinic with newly developed complaints. She has constitutional symptoms, dyspnea, arthralgia of small joints of the hands, morning stiffness lasting almost three hours, oral aphthae at hard palate, Raynaud's phenomenon, and dryness on both mouth and eyes. Her physical examination was revelaed a body temperature of 37.2 Celcius degree, a respiratory rate of 22 per minute, a pulse rate of 10 per minute, blood pressure of 154/92 mm/Hg; oropharyngeal examination revealed a palatal ulcer and crackles extending to bilateral medium lung zones. The cardiovascular system was rhythmic, tachycardic and there was bilateral pretibial edema. She was tendering in some of the small joints of the hands and the wrist. Laboratory tests at the time of rheumatology consultation was summarized in Table 1. Histopathological examination of the renal biopsy specimen showed a WHO class III focal lupus nephritis with an activity index of 19/24. Following the diagnosis of lupus nephritis 15 mg/kg/month cyclophosphamide iv treatment was started along with 3 days of 500 mg pulse methylprednisolone. The steroid was maintained at a dose of 1 mg/kg/day prednisolone. In the 1st month of the treatment, the patient complained of dyspnea requiring oxygen support, and hemoptysis. A thorax CT was consistent with

Table 1. Blood tests (biochemistry, hemogram and autoantibody panel)

	At the first application	At the time of alveolar hemorrhage
BUN (7-18 mg/dl)	39	45
Creatinine (0.6-1.1 mg/dl)	4.42	3.49
Aspartate Aminotransferase (5-34 U/L)	16	18
Alanine Aminotransferase (0-55 U/L)	15	25
CRP (0-5 mg/dl)	1.96	7.01
ESR (<20 mm/h)	124	
WBC (4.000-10.000)	5.130	8.590
Neutrophil (2.000-7.000)	4.480	7.950
Lymphocyte (800-4000)	470	390
Hemoglobin (12-16 g/dl)	9.3	8.3
Platelet (150.000-400.000)	304.000	98.000
Complete urine analysis:	Protein 4+ 20 erythrocytes+	
ANA	Homogeneous positive in 1/1000 titre	
ENA	Anti ds DNA ++ Anti Sm +++ Nucleosome +++ Ro-52 + SS-A +++ Histone ++ nRNP/Sm +++	
ANCA	Negatif	
C3 levels (90-180 mg/dl)	52.9	
C4 levels (10-40 mg/dl)	8.49	
Anti cardiolipin antibodies IG M and G (<7/<10 U/L)	3.0/2.3	
Lupus anticoagulant (0.9-1.1 sn.)	0.96	

BUN: Blood urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC:White blood cell, ANA: Antinuclear antibody, ENA: Extractable nuclear antigens, PR3 ANCA: Proteinase 3 antineutrophil cytoplasmic antibodies MPO ANCA: Proteinase 3 antineutrophil cytoplasmic antibodies

alveolar hemorrhage (Figure 1). Since pneumonia could not be ruled out initially, meropenem and teicoplanin were started. In this application 1 g pulse methylprednisolone treatment was repeated for 3 days, plasma exchange was performed for 5 times as well as 2nd cycle of cyclophosphamide treatment was given and steroid treatment was increased to 2/kg/day prednisolone. In the follow-up, a posteroanterior chest radiographs taken and the findings consistent with alveolar hemorrhage had resolved (Figure 2). After six cycles of cyclophosphamide treatment, the patient was in remission, and she underwent a renal transplantion from a living donor. The patient is now under stable follow-up condition.

Key messages

Vasculitis is seen at a rate of 11-35.9% in SLE and causes serious morbidity and mortality. It usually affects the small, less frequently the medium-sized vessels. Although cutaneous vasculitis is the most common manifestation, it can affect all organs.

Internal organ involvement occurs in about 6–18% of cases of LV according to different series. Even though it is not frequent, visceral involvement is associated with increased mortality.

Treatment modalities vary depending upon the presentation and severity of organ involvement. LV can be fulminant and life-threatening, thus prompt treatment is sometimes became essential.

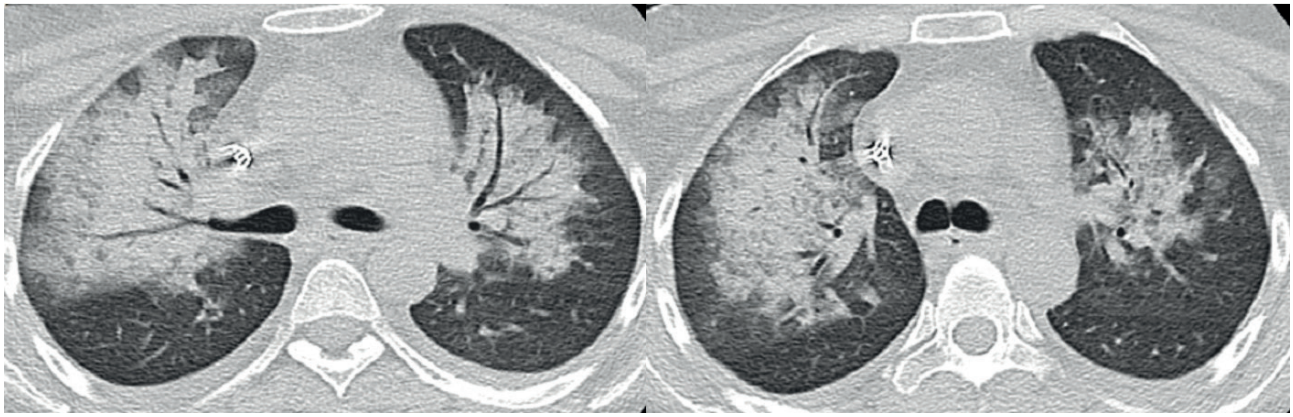

Figure 1. Computed tomographic images of bilateral alveolar infiltrates suggestive of diffuse alveolar hemorrhage.

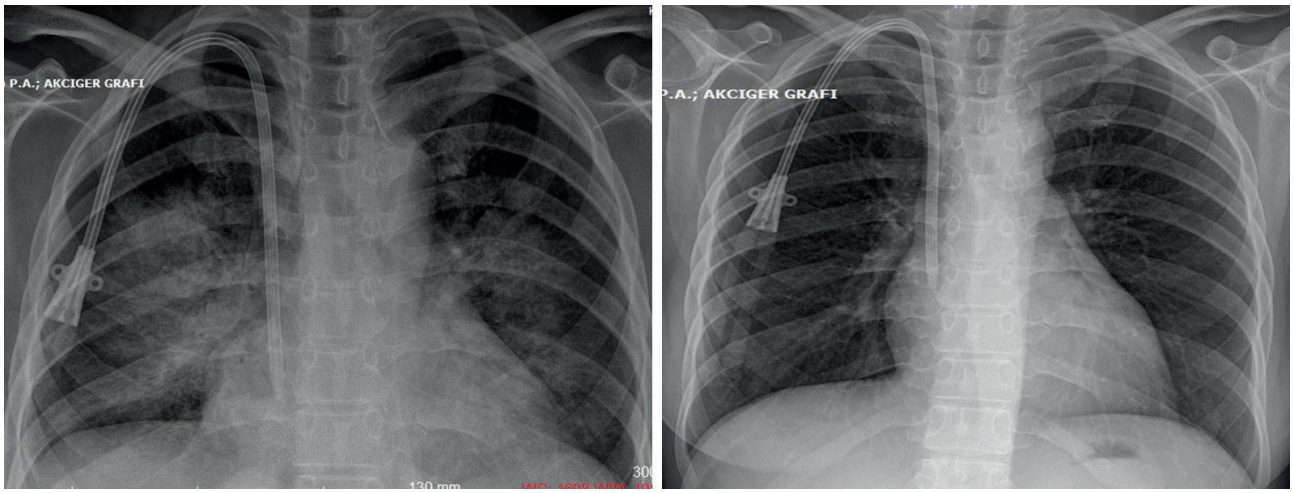

Figure 2. Posteroanterior chest radiographs taken during the active period of alveolar hemorrhage and two weeks later.

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INVITED REVIEWS

Cancer associated vasculitis

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Definition

Cancer-associated vasculitides are classified as 'vasculitides of possible etiologies' according to the Chapel Hill Consensus Conference [1]. All hematological and solid organ neoplasms, clonal B cell lymphoproliferative diseases, and myelodysplastic syndromes (MDS) can cause vasculitides [1]. Used in terminology with probable etiology (e.g. 'ANCA vasculitis associated with gastric cancer') [1]. Paraneoplastic vasculitis terminology is also used in many studies [2]. When the case reports were examined, the most common vasculitis-associated solid tumor was renal cell cancer. In contrast, in the retrospective study of Podjisek et al., the most common was found in lung cancer [3].

Clinical Features

Cancer-associated vasculitis may be a paraneoplastic syndrome, or it may be due to infections, drugs, and cryoglobulin accumulation. In cancer-associated vasculitides, leukocytoclastic vasculitis (LCV) was the most common (45%), followed by PAN (36%) [4]. Leukocytoclastic vasculitis is a histopathological definition of diffuse small vessel vasculitis that can be found in various types of vasculitis affecting the skin and internal organs [3,4].

Diagnosis

It is important to make a good differential diagnosis of both vasculitides and malignancy and to confirm the diagnosis with tissue biopsies [5]. When ANCA-associated vasculitides is associated with hematological malignancies, worse prognosis, more difficult treatment, increased risk of infection, and complications are seen.

Differential diagnosis

The development of vasculitis during cancer may be due to many factors, such as infections, drugs, and cryoglobulin deposition (especially for hematological malignancies). These factors may not be present in approximately 60% of patients.

CASE PRESENTATION

A 44-year-old male patient with no known disease history was admitted to the rheumatology service for further examination and treatment with complaints of rash on bilateral legs, joint pain, and weight loss. He also had rash, nausea, and night sweats for 3 months. Physical examination revealed 3 cm diffuse swelling around the right neck and palpable purpura in both lower extremities (Figure 1). In the laboratory tests, hemoglobin was 11.5 gr/dl (13.5-16.5), leucocytes 8.5 $x10^3$ / µL (3.91-10.9), platelets 195 $x10^3$ / µL (166-300), blood urine nitrogen 15 mg/dl (0-20), creatinine 0.8 mg/dl (0.4-1.2), erythrocyte sedimentation rate (ESR) 54 mm/hour (0-20), C-reactive protein (CRP) level was 105.8 mg/dl (0-5), positive anti-nuclear antibodies (ANA) (1/320 fine speckled pattern), positive proteinase 3 (pr3-ANCA), respectively. His skin biopsy was reported as LCV, and immunofluorescence examination revealed IgA, IgG, and fibrinogen deposits. Cervical lymphadenopathy with 37x27 mm size, thick cortex, heterogeneous internal structure, and peripheral vascularity was detected

in cervical ultrasonography (Figure 2). The nasopharyngeal examination was performed, and a biopsy was performed from the lymphadenopathy present in the cervical. The biopsy examination result of cervical lymphadenopathy was reported as low-grade B-cell lymphoid neoplasia. Also, the bone marrow biopsy resulted in a transformation from chronic lymphocytic leukemia to Hodgkin lymphoma. As a result of F-18 fluorodeoxyglucose positron emission tomography (FDG- PET), the patient was diagnosed with early-stage Hodgkin lymphoma (ESHL). He was started on conventional chemotherapy for Hodgkin lymphoma.

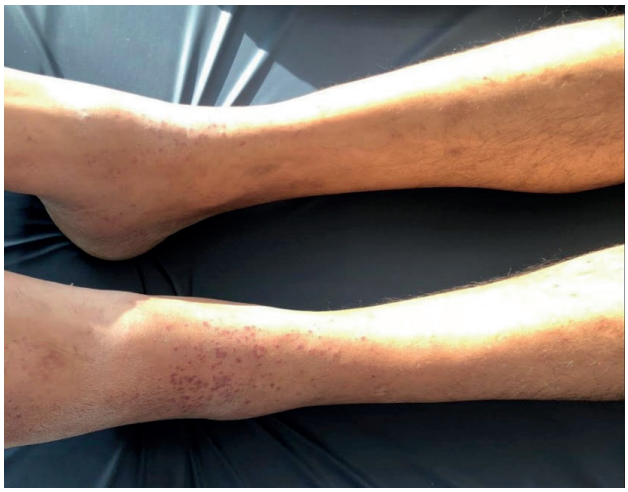

Figure 1. Palpable purpura in both lower extremities.

Key messages

- Clinicians rarely encounter malignancy in the etiology of cutaneous vasculitides.
- Whether this is an etiological cause or a paraneoplastic condition is still being discussed.
- most common underlying malignancy is usually hematological malignancy.
- The prognosis varies depending on the underlying neoplasia.

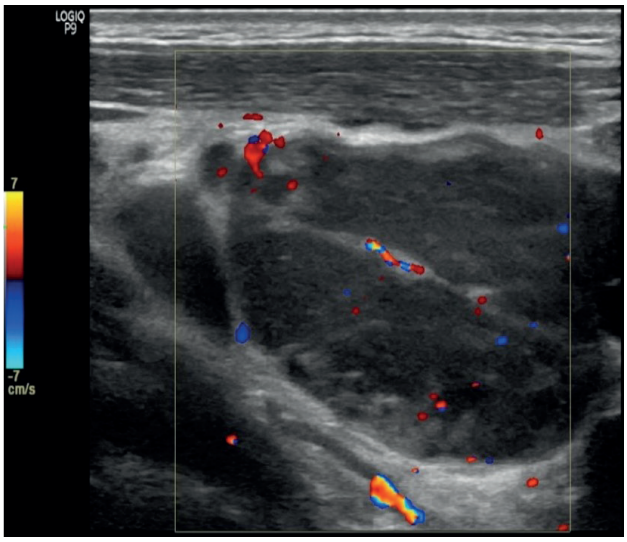

Figure 2. Cervical lymphadenopathy with 37x27 mm size, thick cortex, heterogeneous internal structure, and peripheral vascularity.

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INVITED REVIEWS

Cutaneous arteritis: Description based on Chapel Hill Conference Consensus 2012 and a case report

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Definition

According to the overview of the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCCNV), cutaneous polyarteritis nodosa (cPAN) has been reclassified as cutaneous arteritis (CA), a form of single-organ vasculitis [1]. Single-organ vasculitis refers to vasculitis that exclusively affects one organ and lacks systemic involvement. CA specifically targets the skin and is characterized by involvement of small to medium-sized blood vessels [2]. Clinical manifestations encompass subcutaneous nodules, livedo reticularis, ulcers, and purpura. This chronic, recurring vasculitis primarily affects the small arteries and arterioles at the panniculus and the dermal-subcutaneous junction. Diagnosis relies on recognizing typical skin lesions, the absence of systemic symptoms, and corroborative histopathological findings [3].

Etiology

CA is a rare disease, and the true incidence is unknown. This cutaneous vasculitis affects patients of all ages, and there is no gender predominance.

The cause of CA remains uncertain. It might emerge from an underlying condition, infections (such as group A β hemolytic streptococcus, hepatitis B, hepatitis C, parvovirus B-19, and mycobacterium tuberculosis), or drug usage (notably, minocycline-induced cPAN has been well-documented) in around 10-15% of instances. Additionally, malignancies contribute to the vasculitis's onset in 5% of cases, involving both hematologic and solid organ malignancies [2,4].

Connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, sjögren syndrome) and inflammatory diseases (inflammatory bowel diseases, cryoglobulinemia type 2 and 3, antineutrophilic cytoplasmic antibody (ANCA)-related vasculitis and Behçet's disease) are the etiologic factors in 15–20% of the cases. An association between cPAN and inflammatory bowel disease has been established in a case series. Among 79 patients diagnosed with cPAN, 5 cases were also diagnosed with inflammatory bowel disease (comprising four cases of Crohn's disease and one case of ulcerative colitis) [5,6].

Clinical Features

CA typically manifests initially as livedo reticularis (in 56% of cases), along with tender subcutaneous nodules or skin ulcerations. Additional observed symptoms encompass purpura, cutaneous necrosis, and localized extracutaneous manifestations. The condition primarily affects the legs, followed by the arms and trunk [4].

It usually has a benign course but usually, relapses occur, especially in patients with ulcers and increased acute phase reactants. Extra-cutaneous manifestations of CA include constitutional symptoms such as myalgias, arthralgias, and neuropathy, but these are not the evidence of a systemic disease [5].

Diagnosis

The current diagnostic criteria for cPAN were proposed in 2009 by Nakamura et al., and include the presence of cutaneous manifestations and histopathological findings without systemic involvement [3]. The diagnosis is based on typical lesions in a deep incisional cutaneous biopsy, as there are no specific serological tests. Direct immunofluorescence (DIF) frequently reveals the presence of IgM and C3 deposits within the affected arterial walls, indicating its association with immune complex-mediated pathology.

Treatment

Treatment choice dependes on the severity of skin lesions. Non-steroidal anti-inflammatory drugs and colchicine may be preferred in mild to moderate cases. In cases that prove refractory and involve severe pain, ulcers, or necrosis, treatment options often include prednisolone (30-60 mg/day), hydroxychloroquine, dapsone, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, sulfapyridine, pentoxyphylline, and intravenous immunoglobulin. It is important to note that there is no treatment with established efficacy through prospective trials [7].

Differential diagnosis

CA must be distinguished from systemic (PAN) sPAN is characterized by identical cutaneous findings and the presence of systemic organ involvement including liver, kidney, and heart. The extra-cutaneous manifestations of peripheral neuropathy and myalgia in CA can occur only in adjacent to the cutaneous lesions, while they may be disparate in systemic PAN [3].

Furthermore, it's crucial to differentiate from other forms of vasculitides, such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatous polyangiitis (EGPA), erythema induratum, and urticarial vasculitis (Table 2) [5]. GPA and EGPA also affect small- to medium-sized vessels. Pulmonary involvement, granulomatous inflammation, and anti-neutrophil cytoplasmic antibody (ANCA) positivity are common in both. MPA typically affects small vessels, in the kidneys and lungs. Urticarial vasculitis is also a small-vessel vasculitis demonstrated with painful burning urticaria (lasting longer than 24 hours) and arthralgias, which do not occur in CA.

CASE REPORT

A twenty-one-year-old woman presented with a complaint of painful subcutaneous erythematous nodules on both her upper and lower extremities, persisting for a duration of five months. There was no history of purpura, Raynaud's phenomenon, recurrent oral ulcers, hair loss, or malar rash. On physical examination, she had multiple

Table 1. A new draft of diagnostic criteria for cutaneous polyarteritis nodosa [3]

1. Cutaneous manifestations
Subcutaneous nodules, Livedo, Purpura, Ulcers
2. Histopathological findings
Fibrinoid necrotizing vasculitis of small and medium-sized arteries
3. Exclusion manifestations
(1) Fever (=38°C, =2 weeks), Weight loss (6 kg or more in 6 months)
(2) Hypertension
(3) Rapidly progressive renal failure, Renal infarction
(4) Cerebral hemorrhage, Cerebral infarction
(5) Myocardial infarction, Ischemic heart disease, Pericarditis, Heart failure
(6) Pleuritis
(7) Intestinal hemorrhage, intestinal infarction
(8) Peripheral neuropathy out of the affected skin lesion
(9) Arthralgia (arthritis) or myalgia (myositis) out of the skin lesion
(10) Abnormal arteriography (multiple microaneurysms, stenosis, and obliteration)
4. Decision
Both cutaneous manifestations and histopathological findings without exclusion manifestations

Table 2. Differential diagnosis and questioning of cutaneous vasculitis [5]

Systemic polyarteritis nodosa	Medium-sized arterial vasculitis, punched out ulcers, hypertension, renal failure, hematuria, abdominal pain, and microaneurysms on MRI
Microscopic polyangiitis	Small and medium-sized vessel vasculitis, involving the kidneys and lungs. Palpable purpura, constitutional symptoms, glomerulonephritis, alveolar hemorrhage, and p-ANCA>c-ANCA
Eosinophilic granulomatosis with polyangiitis	Granulomatous vasculitis, asthma, allergic rhinitis, palpable purpura, subcutaneous nodules, peripheral eosinophilia, and p-ANCA
Granulomatosis with polyangiitis	Necrotizing granulomatous small vessel vasculitis, cutaneous and oral ulcerations, upper and lower respiratory tract involvement, glomerulonephritis and c-ANCA
Livedoid vasculopathy	Superficial dermal vasculopathy, atrophie blanche with peripheral telangiectasia and punched out ulcers on ankles
Erythema induratum	Lobular or mixed panniculitis small or medium-sized vessel vasculitis, erythematous nodules and plaques that may ulcerate on dorsal legs
Urticarial vasculitis	Leukocytoclastic vasculitis, and urticaria lasting >24 hours.

subcutaneous ulcers predominantly distributed over all extremities. Laboratory tests including complete blood count, liver and kidney function tests, and serum complement levels were within normal ranges. Anti-nuclear antibody (ANA), ANCA, and rheumatoid factor (RF) were negative. Histopathologic examination of the subcutaneous nodule revealed neutrophilic vasculitis of the dermal medium and small vessels (Figure 1).

The patient was treated with methylprednisolone of 20 mg/day and colchicine of 1 mg/day. Methylprednisolone was tapered and discontinued in the 3rd month. The lesions completely resolved over a period of three months and the patient was on regular follow-up. Colchicine treatment was discontinued after 2 years and then she was in remission. There was no new lesion at the last control (in the 4th year of the disease) 1 month ago.

Key messages

- Cutaneous arteritis (previously known as cutaneous polyarteritis nodosa) is an uncommon form of single-organ vasculitis that targets the deep skin vessels and subcutaneous tissue
- This condition tends to be chronic and benign, occasionally exhibiting a relapsing pattern.
- Diagnosis relies on recognizing the characteristic clinical and histopathological traits.
- The seriousness of the skin manifestations determines treatment approaches; however, it's important to note that there is no treatment with proven efficacy based on prospective trials.

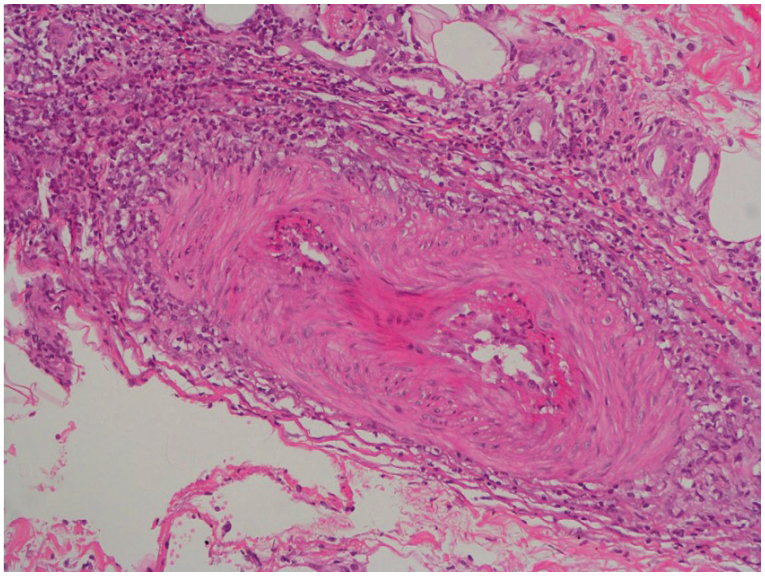

Figure 1. Mild fibrinoid necrosis with moderate vessel wall thickening and inflammatory infiltrate of lymphocytes and neutrophils advancing to the vessel wall.

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INVITED REVIEWS

Primary central nervous system vasculitis: Description based on Chapel Hill Conference Consensus 2012 and a case report

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INTRODUCTION

Primary central nervous system vasculitis (PCNSV) is an uncommon form of vasculitis that predominantly affects small and medium-sized blood vessels of the brain parenchyma, spinal cord, and leptomeninges. It is difficult to estimate the true incidence rates due to the diagnostic difficulties. The diagnostic criteria recommended for the diagnosis of PCNSV have yet to be validated due to the rarity of the disease. PCNSV is among the single-organ vasculitis (SOV), and systemic diseases with cerebral vascular involvement should be excluded before the diagnosis. Initial symptoms may be acute or subacute and nonspecific. Most affected cases may present with recurrent vascular events, cognitive dysfunction, headache, and seizures. Nonspecific presentations lead to delays in diagnosis, complications, and poor prognosis. This article aims to highlight the specific clinical, laboratory, and imaging features of PCNSV and presents a case report.

Definition

Single-organ vasculitis refers to vasculitis in arteries or veins of any size in a single organ. There should be no feature of systemic vasculitis, infection, or systemic disease [1]. When vasculitis findings are observed in a single organ, if there is an impression that it is a limited form of systemic vasculitis, it is not categorized as SOV. Clinical, laboratory, and pathological features help distinguish SOV from systemic vasculitis with isolated organ involvement [2].

The involved organ and vessel type should be included in the name [3]. Some SOV cases may show clinical manifestations of systemic vasculitis in the later stages of the disease. In this case, the categorization of the disease also changes.

Epidemiology

PCNSV is a rare disease, and the cause is unknown. Its incidence is reported as 2.4 cases per million per year [4]. It is difficult to estimate the true incidence rates due to the low awareness and diagnostic difficulties. In a study conducted in the USA, it was determined that annual hospitalization of the disease is 5.1 cases per 1.000.000 person-years [5]. It is observed twice as often in men [6,7]. Although it can be seen at any age, the median age at diagnosis is 50 years [4,7].

Clinical Features

PCNSV can affect any part of the central nervous system, so the symptoms are varied and nonspecific. Symptoms can be acute or insidious. But in most cases, there is a long prodromal period [7]. PCNSV does not have a pathognomonic clinical picture and may present with non-specific symptoms. Headache is often the first symptom but can also occur with stroke-related focal deficits [8]. There

is no typical type of headache in PCNSV, but "thunderclap headache" is rarely seen. Reversible cerebral vasoconstriction syndrome (RCVS) should be considered when this type of headache is present [8].

Other clinical conditions include; recurrent vascular events, cognitive dysfunction, and seizures. PCNSV should be considered when recurrent stroke and transient ischemic attack occur in young patients without risk factors for atherosclerosis and hypercoagulability [9].

Diagnosis (Radiology & Pathology)

The diagnostic criteria recommended for the diagnosis of PCNSV have yet to be validated due to the rarity of the disease [10]. These criteria;

- Presence of unexplained neurological deficit after detailed clinical and laboratory evaluation,
- Evidence of either vasculitic process in the central nerve system (CNS) by cerebral angiography and/or histopathology,
- Absence of evidence of another systemic vasculitis or other condition with which angiographic or pathological abnormalities may be associated.

There is no specific laboratory or imaging method for the diagnosis of PCNSV. Therefore, a comprehensive diagnostic examination is recommended. This diagnostic examination includes neuropsychiatric evaluation, blood and cerebrospinal fluid analysis, brain magnetic resonance imaging, and angiographic modalities [11].

Various neuroimaging modalities can be used to assess for both parenchymal and vascular abnormalities in the evaluation of possible PCNSV [7]. The first step in diagnosis is brain MR imaging to monitor the lesions. High-resolution magnetic resonance vessel wall imaging (HRVWI) is a promising new imaging modality for diagnosis [12,13], but its use is currently limited.

Angiographic and/or histological evidence of vasculitis is required as the next step. Although angiographic methods are not pathognomonic for PCNSV, they can detect segmental narrowing of vascular structures. It is useful in excluding alternative diagnoses such as atherosclerosis, moyamoya disease, and dissection [7].

Histopathological evaluation is still the gold standard diagnostic method for PCNSV [7]. In addition, it is very useful in terms of excluding possible causes. In a meta-analysis, biopsy demonstrated a diagnostic yield of 74.7% (95% confidence interval [CI] 64.0-84.1%) for a suspected diagnosis of PCNSV [14]. However, it should be kept in mind that segmental inflammation may reduce the sensitivity of the biopsy [9].

Differential Diagnosis

The differential diagnosis of PCNSV includes viral and bacterial infections, demyelinating and neoplastic diseases, and other inflammatory lesions of the CNS [13]. In such cases, primarily infectious and malignant processes should be excluded.

The absence of signs and symptoms suggestive of systemic vasculitis, such as fever, weight loss, rash, or peripheral neuropathy, and negative immunological marker results indicate that vasculitis is primary. Differentiation from systemic vasculitis or other autoimmune diseases is important in terms of investigating other organ involvements and choosing treatment.

Management

There are no controlled, randomized, prospective studies to guide PCNSV management. Treatment of PCNSV should be individualized according to the severity and the extent of the neurologic deficit. Usually, the recommended treatment scheme is similar to polyarteritis nodosa [7]. In addition to systemic corticosteroids, cyclophosphamide or rituximab are preferred in induction treatment. Prednisone is initiated at high doses, usually around 1 mg/kg or 60 mg daily, and tapered over months. Cyclophosphamide can be used orally or intravenously and usually lasts 3-6 months [8]. Some clinicians recommend continuing treatment with azathioprine and mycophenolate mofetil as maintenance therapy [8]. The use of oral immunosuppressive agents for maintenance after induction therapy has resulted in prolonged remission [13,15]. Symptoms, neurological findings, and radiological imaging are important in the follow-up of treatment. If treatment failure is experienced after appropriate treatment, a re-evaluation should be performed, and alternative diagnoses should be reviewed.

Prognosis

This rare form of vasculitis, which is difficult to recognize, results in severe morbidity and mortality if not treated aggressively with immunosuppressive agents. Because it is a highly heterogeneous disease, its prognosis is variable. The relapse rate is around 25-30%, but there are also publications reporting it as 55%. [16-18]. The presence of small vessel vasculitis and lesions with high gadolinium involvement is associated with a high relapse rate, whereas the use of oral maintenance therapy and the presence of headache at disease onset is associated with a low relapse rate risk. [13]. In one study, approximately 35% of cases were discharged to a rehabilitation center, while 5% died before discharge [5]. Mortality has been reported as 6-16% [16-17].

CASE PRESENTATION

Abstract

Herein, we would like to present a case of PCNSV with a focal mass lesion as a preliminary diagnosis in cross-sectional imaging and diagnosed with vasculitis by biopsy.

Keywords: Central nervous system, vasculitis, focal mass lesion.

A 41-years-old male patient presented with dysphasia, facial asymmetry, peripheral sensory deficit, and weakness in the left upper and lower extremities. The symptoms started a few months ago. There was no history of oral aphthae and genital ulcer active/scarring and uveitis. Physical examination revealed left hemihypoesthesia/hemiparesis with findings consistent with left facial paralysis. Laboratory findings were normal except for mild acute phase elevation (Crp: 10.5 mg/L, reference range 0-5 mg/L). Immunological marker results were negative (Table 1).

Brain Magnetic Resonance Imaging (MRI) revealed a focal mass lesion starting from the thalamus level to the mesencephalon in the deep white matter of the right hemisphere at the supratentorial level. The focal lesion is T2 FLAIR hyperintense and indistinguishable in T1 with patchy contrast enhancement (Figure 1). A stereotaxic biopsy was performed by neurosurgery.

After fixation of the biopsy specimen with 10% formaldehyde, it was embedded in paraffin. Afterward, sections with a thickness of 5µm were taken and examined by staining with Hematoxylin-Eosin. Inflammatory infiltration consisting of lymphocytes, histiocytes, and rare eosinophils was observed in the perivascular areas and vessel walls (Figure 2). It was determined that lymphocytes concentrated around the vascular structures were extensively stained with immunohistochemical CD3 and not with CD20. Findings were interpreted as vasculitis and secondary brain parenchyma involvement.

Pulse steroid therapy was administered at a dose of 1 g/day methylprednisolone for three days. Afterward, oral methylprednisolone at a dose of 1 mg/kg was started. As remission induction therapy, cyclophosphamide 1000 mg intravenously was given for 6 cycles every 21 days. After the completion of the induction therapy, maintenance immunosuppressive therapy was initiated with azathioprine at a dose of 2 mg/kg. Corticosteroid treatment was discontinued due to clinical and radiological complete response after one year of treatment. The maintenance immunosuppressive treatment of the patient, who was followed up in complete remission, was also discontinued at the end of the third year.

Table 1. Laboratory findings at admission

	Laboratory results	Reference range
Hemoglobin (g/dl)	15.5	12-16
Leukocyte count (10^3/mm^3)	8.14	4-1
Platelet count (10^3/mm^3)	387	150-450
C-reactive protein (mg/L)	10.5	0-5
Erythrocyte sedimentation rate (mm/h)	11	0-20
Creatinine (mg/dl)	0.96	0.7-1.3
GFR (CKD-EPI) (ml/min)	97	60-150
Proteinuria (UPCR)(mg/mg)	0.07	<0.2
Albumin (gr/dl)	4.7	3.5-5.2
ANA	Negative	-
ANCA	Negative	-
HLA-B51	Negative	-
C3 mg/dl	139	90-180
C4 mg/dl	27	10-40

GFR, Glomerular filtration rate; UPCR, urine protein/creatinine ratio; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; HLA-B51, Human leucocyte antigen-B51; C3, complement 3; C4, complement 4.

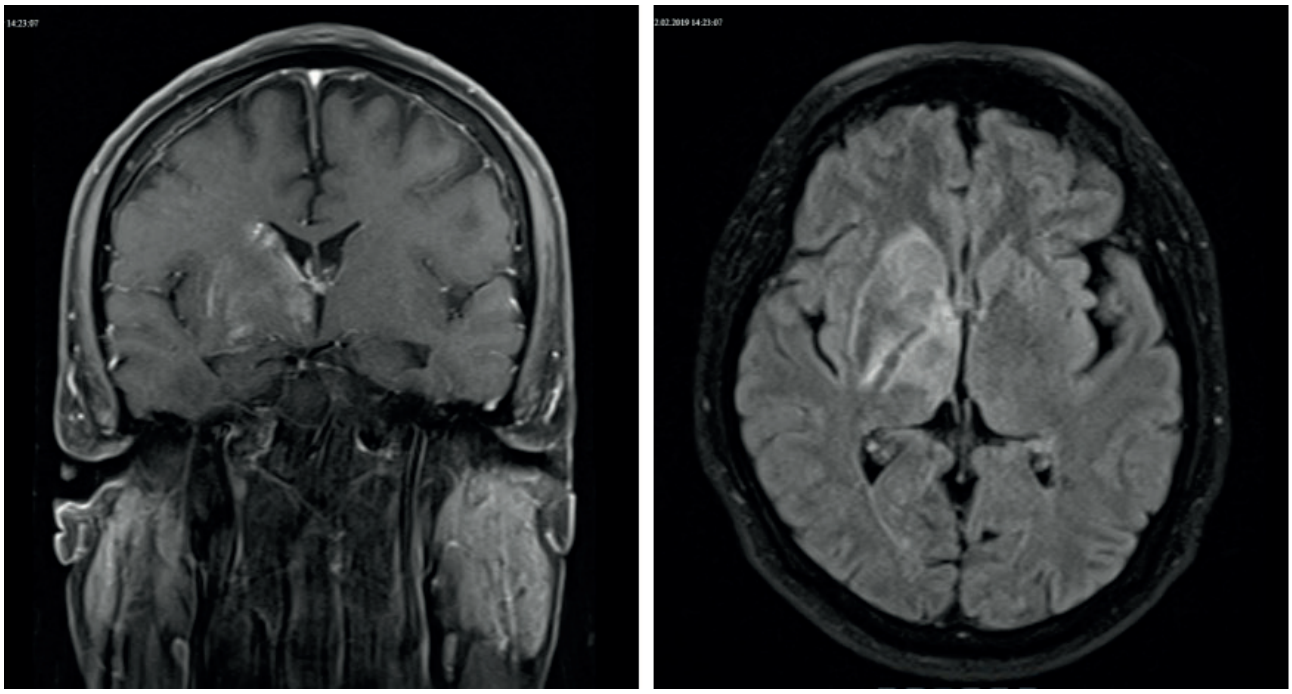

Figure 1. T2W hyperintense focal mass lesion observed in the right hemisphere on frontal and sagittal sections.

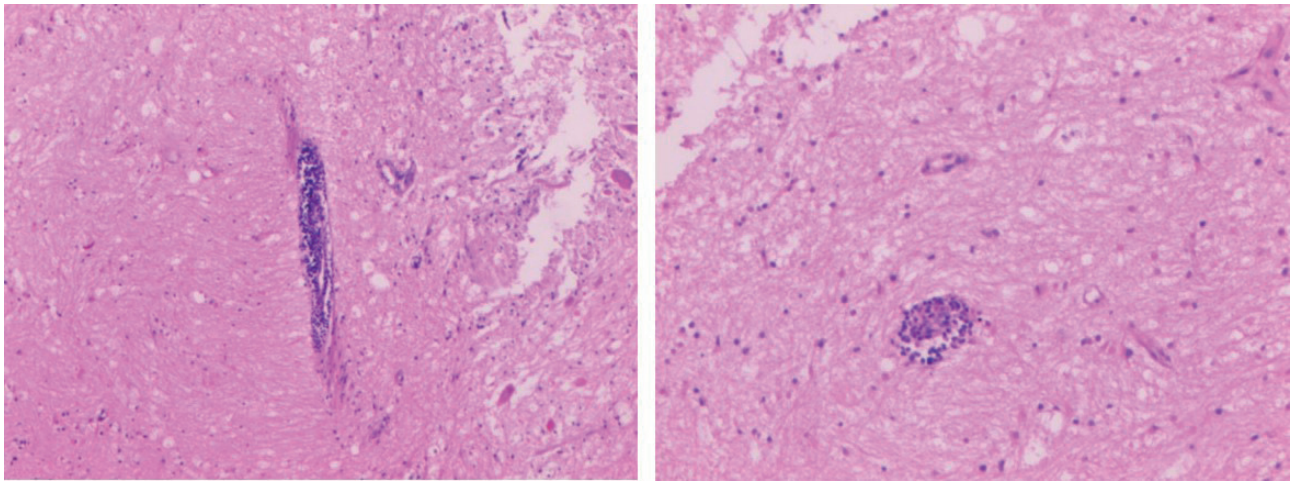

Figure 2. Inflammatory infiltration consisting of lymphocytes, histiocytes, and rare eosinophils was observed in the perivascular areas and vessel walls.

Key messages

- PCNSV is a rare form of vasculitis that causes heterogeneous clinical presentations.
- Due to the rarity of the disease, the diagnostic criteria could not be validated. They are diseases that can result in serious morbidity and mortality if not treated with immunosuppressives.
- Establishing consensus in diagnostic processes and treatment management, making algorithms, and determining their differences from secondary vasculitides are important goals.

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INVITED REVIEWS

Romatoid vasculitis: Definition based on Chapel Hill Conference Consensus 2012

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease that progresses with synovial inflammation [1]. Rheumatoid vasculitis is a rarely seen but serious complication, observed especially in seropositive patients with long disease duration [2-4]. As RA's most severe extra-articular complication, rheumatoid vasculitis generally affects small and medium-diameter arteries and has high morbidity and mortality rates [5,6]. Although rheumatoid vasculitis can involve all organs, findings are most often seen in the form of skin and peripheral nervous system involvement. As there is no specific finding, the exclusion of other causes of vasculitis and the histopathological observation of necrotizing vasculitis is required for diagnosis [6,7].

Definition

In the Chapel-Hill consensus, rheumatoid vasculitis and systemic diseases are included in the secondary vasculitis group. According to this classification system, rheumatoid vasculitis should be considered in the presence of vasculitic lesions in patients with RA [8].

Classification

There are no validated diagnostic or classification criteria for rheumatoid vasculitis. Patients diagnosed with RA should have at least one of the 4 findings stated in the criteria recommended by Scott and Bacon in 1984, and other causes should be excluded. The findings in these criteria, which have not yet been validated, are as follows [3,6,9-11];

1. Mononeuritis multiplex or peripheral neuropathy
2. Peripheral gangrene
3. The biopsy finding of necrotizing arteritis accompanying systemic disease
4. Active extra-articular diseases such as pleuritis, pericarditis, and scleritis associated with biopsy findings of deep skin ulcers or typical digital infarct or vasculitis.

Epidemiology

Active vasculitis develops in approximately 1-5% of RA patients with disease duration longer than 10 years [4,6,10]. Cases have been reported at rates of 15%-31% in autopsy series [12]. However, it has also been reported that the incidence of rheumatoid vasculitis has decreased from 9.1 to 3.9 per million because of effective treatment modalities in the last 30 years. Many risk factors for rheumatoid vasculitis have been reported, including male gender, smoking, long duration of RA, rheumatoid nodules, and HLA class I and II genotype. Patients with Felty syndrome are known to tend to develop vasculitis [2,6,11,13-15].

Clinical Features

As many organs can be affected by rheumatoid vasculitis, which is the most serious complication

of RA, it can present with different findings. Unlike patients with lupus vasculitis, these patients have low disease activity. Extra-articular involvement, such as rheumatoid nodules and erosive disease, are present in patients. Skin involvement is the most common form, and there are skin findings in approximately 90% of cases. Petechiae, purpura, skin ulcers, and gangrene may be seen, and patients may also have general constitutional findings such as fever and weight loss [3,11,15-17]. In approximately half of the patients, peri and/or epineural arteritis associated with necrotizing vasculitis and associated acute, symmetrical, peripheral nerve lesions may develop. There may also be involvement of the heart, lungs, kidneys, gastrointestinal system, and central nervous system [3,4,10] (Table 1).

Diagnosis

It can be difficult to diagnose a patient presenting with findings of vasculitis if the diagnosis of RA is not known. The presence of skin lesions or neurological findings in a seropositive RA patient should be a warning in respect of rheumatoid vasculitis. The medical history, physical examination, laboratory tests, and histopathological examination may be necessary for diagnosis. Histopathological evaluation is important for diagnosis and the decision for aggressive treatment when necessary [3,6,11].

Although there is no specific laboratory test for the diagnosis of rheumatoid vasculitis, anti-cyclic citrullinated peptide (ACPA) positivity with RF at high titers, hypocomplementemia, and cryoglobulinemia may be detected in

Table 1. Clinical presentation of rheumatoid vasculitis [3]

Organ system	Presentation	Prevalence
Skin	Nail fold infarcts Purpura Non-healing ulcers Digital ischemia Livedo reticularis Pyoderma gangrenosum Rheumatoid nodules	90%
Peripheral nervous system	Sensory / motor / mixed polyneuropathy Mononeuritis multiplex	40%
Heart	Pericarditis / Myocarditis Coronary arteritis Aortitis	30%
Eye	Scleritis / Episcleritis Peripheral ulcerative keratitis Retinal vasculitis	16%
Gastrointestinal involvement	Mesenteric vasculitis Bowel ischemia Arteritis of the liver, pancreas, spleen, gallbladder	10%
Lung	Diffuse alveolar hemorrhage Pleuritis Fibrosing alveolitis	Rare
Kidney	Interstitial nephritis Pauci-immune glomerulonephritis Testicular vasculitis	Rare
Central nervous system	Seizures Strokes Myelopathy Hypertrophic meningitis Central nervous palsies	Rare

most patients. In addition, findings supporting inflammation may be determined, such as acute phase reactant elevation, thrombocytosis, anemia, hypoalbuminemia, and hypergammaglobulinemia. Therefore, in addition to routine biochemistry, complete blood count, urine analysis, and acute phase reactants at the time of diagnosis, RF, ACPA, complement, and immunoglobulin levels should also be requested. To exclude other secondary vasculitis causes, hepatitis markers, anti-HIV, antinuclear antibodies, and anti-neutrophil cytoplasmic antibodies (ANCA) should also be examined. Moreover, it must not be forgotten that there may be perinuclear ANCA (generally lactoferrin) positivity in 36%-48% of patients with rheumatoid vasculitis [3,4,11,15].

In addition to the diagnosis, evaluation of the extent of organ involvement is important, and when necessary ophthalmological evaluation, electrocardiography, and electromyography should be performed [3,11].

Radiology: Depending on the organ involved in rheumatoid vasculitis, mesenteric angiography, thorax computed tomography (CT), or cranial magnetic resonance imaging (MRI) can be requested [3].

Pathology: Involvement of small to medium-diameter arteries is seen in rheumatoid vasculitis. Postcapillary venules are more often involved, and although IgG/IgM accumulation is usually seen, there may also be IgA accumulation. Postcapillary venules are more often involved than large vessels and are important in the differentiation of actual IgA or IgG/IgM vasculitis. Histopathologically, mononuclear cells, neutrophil infiltration in the vessel wall, and fibrinoid necrosis are determined. Findings of destruction, such as leukocytoclasis and necrosis in the vessel wall, are often observed [6,11,15,17].

Differential diagnosis

Other forms of vasculitis must be reviewed in the differential diagnosis of patients presenting with rheumatoid vasculitis. In patients presenting with skin findings such as purpura and petechiae in the lower extremities, a differential diagnosis should be made for idiopathic thrombocytopenic purpura, hypersensitivity vasculitis, and Henoch-Schönlein purpura and for patients with pulmonary, renal, and nervous system involvement, pulmonary-renal syndromes should be kept in mind, primarily ANCA-related vasculitis. As there are reports of rheumatoid vasculitis cases related to biological treatments such as anti-TNF and tocilizumab, patients must be evaluated in respect of drug-related vasculitis [3]. Another type of vasculitis involving small-medium diameter arteries is polyarteritis nodosa (PAN), which can sometimes be confused with rheumatoid vasculitis. In the differentiation from PAN, the observation of postcapillary venule involvement, RF positivity, and the presence of arthritis are important [6,17].

Management

In the literature, there are no randomized, controlled studies of rheumatoid vasculitis as it is rarely seen and there are no validated criteria. There are case reports and case series in which more empirical treatments have been given, and many treatments have been attempted including plasma exchange and IVIG. In patients with mild and moderate severity (rheumatoid vasculitis limited to the skin), treatment with disease-modifying anti-rheumatic drugs (DMARDs) such as moderate-dose steroid and methotrexate, azathioprine or leflunomide may be sufficient [3,10]. However, in cases with severe involvement, treatment is recommended of induction with cyclophosphamide in addition to high-dose steroids, followed by maintenance with DMARDs. Other biological treatments such as rituximab or anti-TNF agents, tocilizumab, and abatacept have been attempted in refractory patients, and positive results have been obtained [6,9,10,13,18].

Prognosis

Recurrence is common in rheumatoid vasculitis; the 5-year mortality rate has been reported to be between 30% and 60%. Disease-related complications and treatment-associated toxicity are among the causes that increase mortality [3,10,14].

CASE

Abstract:

Rheumatoid vasculitis is an uncommon long-term complication of rheumatoid arthritis. Although cases are often seen in the form of cutaneous

vasculitis, mononeuritis multiplex because of necrotizing vasculitis of vaso nervorum is also observed. Herein, a rheumatoid vasculitis case with mononeuritis multiplex is presented.

Case Presentation:

A 58-year-old male patient presented at the Neurology Outpatient Clinic with complaints of weakness in the legs. Complaints of pain and swelling in both hands' metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints started 10 years ago. At that time, morning stiffness lasted for approximately 1 hour. He was diagnosed as RA in another center and treatment was started with methotrexate (MTX) 15mg/week and methylprednisolone 4mg. Throughout the 10-year period, the patient had taken the drugs irregularly and had not attended regular follow-up appointments. In the last 2 years, the patient had taken steroids only and in the last 6 months, had taken MTX regularly. The complaints of weakness, pain, and numbness in the right lower extremity had started 1 month previously, and after 10 days, similar complaints developed in the left lower extremity. The patient was admitted to the Neurology Clinic.

On EMG, signal loss was determined at an advanced level in the bilateral peroneal nerves below the knee. On cervical spinal MRI, there was central-right paramedian protrusion not causing spinal canal pressure at the C4-C5 level, minimal diffuse bulging at C3-C4 and C5-C6 levels, and on lumbar spinal MRI, diffuse bulging and disc degeneration was determined at L4-L5 and L5-S1 levels, but no narrowing was determined in the spinal canal and neural foramen. The thorax CT examined in respect of malignancy was determined to be normal, and on the abdominal CT, stones were observed in the right kidney. On echocardiography, ejection fraction of 70%, left ventricle hypertrophy and relaxation impairment were determined, and normal left ventricle systolic functions.

Muscle-nerve biopsies were performed for the diagnosis of mononeuritis multiplex. In the nerve biopsy there was reported to be axonal degeneration in the nerve fibers, fibrinoid necrosis in the vascular structures of the nerve, and inflammatory cells such as neutrophils, lymphocytes, and histiocytes in the vessel wall. It was reported as necrotizing vasculitis and progressive axonal degeneration. Mononeuritis multiplex due to vasculitic neuropathy was considered by the neurology specialist so treatment was started with methylprednisolone 60 mg/day and gabapentin 300 mg/day. Our department was consulted and the patient was transferred to our clinic with the diagnosis of RA-related vasculitis. In the physical examination of the patient, swelling was observed in the 4th finger PIP joint of the right hand and in the 2nd, 3rd, 4th, and 5th finger PIP joints of the left hand. The proximal and distal muscle strength of the upper extremities were normal. However, the distal muscle strength of the lower extremities were 1/5 while the proximal sides were normal. In addition, decreased superficial and vibration senses in bilateral ankles, hypoesthesia in the distal lower extremities were detected. Deep tendon reflexes were normoactive and pathological reflexes were absent. Laboratory results: erythrocyte sedimentation rate: 65 mm/hr, C-reactive protein: 199 mg/dl, rheumatoid factor: 604 IU/ml, anti-CCP: 200 U/ml, anti-nuclear antibody (ANA): negative (-), ANCA: negative (-), EBV IgM (-), CMV IgM (-), Toxo IgM (-), HbsAg (-), anti HCV (-), anti HIV (-), VDRL (-), and the TSH, vitamin B12, and folic acid value were within normal limits.

The patient was treated with 1 gr cyclophosphamide because of vasculitis, and the steroid and gabapentin treatment were continued. The patient was referred to the Physical Therapy and Rehabilitation Department because of drop foot, was given bilateral plastic rest moulds, and underwent physical therapy rehabilitation, but the foot dorsiflexion and plantar flexion of the patient remained limited. After the completion of 6 cycles of cyclophosphamide treatment, the treatment was continued with azathioprine 150 mg/day, hydroxychloroquine 200 mg/day, and methylprednisolone 4 mg/day. As the joint complaints continued during the follow-up, leflunomide 20mg/day was added to the treatment. Under this treatment, the joint complaints recovered and there were no additional complaints. Until 2015, the patient attended follow-up visits irregularly, after which there was no follow-up. It was learned that the patient died because of COVID-19 infection in 2020.

Key Messages

- Rheumatoid vasculitis is the most severe extra-articular complication of RA and has high morbidity and mortality rates.
- Generally, small and medium sized arteries are affected.

– Although many organs are affected, skin involvement is most common.

– It is seen especially in male patients who are smokers with erosive disease of long duration

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INVITED REVIEWS

Syphilis aortitis in the differential diagnosis of aortitis: When should we suspect?

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Syphilis is a systemic disease caused by Treponema pallidum. It is most commonly transmitted by sexual contact, rarely by transplacental/perinatal and blood transfusion, and can cause serious morbidity and mortality [1]. Syphilis can be divided into four stages according to clinical signs and symptoms.

a) Primary Syphilis: It occurs as a painless, round, initially shiny ulcer in the genital area. Enlargement is detected in lymph nodes close to the ulcer site. Syphilis is very contagious during this period. The ulcer, called chancre, heals spontaneously within 6 weeks [1].

b) Secondary Syphilis: Approximately 25% of individuals with untreated primary infection develop symptoms that can mimic any skin disease in the following 2 years. Diffuse, symmetrical macular or papular rashes involving the whole trunk and extremities, systemic symptoms such as fever, headache, malaise, anorexia, sore throat, myalgia, weight loss, renal pathologies such as diffuse lymphadenopathy, hepatitis, acute renal failure, nephrotic syndrome, acute nephritis, neurological abnormalities and ocular abnormalities such as uveitis (most often posterior), retinal necrosis, optic neuritis can be seen during this period. Ocular abnormalities may also be a manifestation of neurosyphilis [1].

c) Latent Syphilis: It is the serological infection period without any signs of disease. There is no contagiousness.

d) Tertiary Syphilis: The period observed after approximately 15 years in untreated patients. This period is rare nowadays. Involvement of the ascending aorta, which classically presents with an aneurysm in the cardiovascular system, may rarely cause dissection. In tertiary syphilis, granulomatous-nodular lesions are observed in the skin, bone, and visceral organs. Central nervous system involvement may occur at any stage of syphilis, tabes dorsalis and paresthesia may be seen [1]. All cases of syphilis should also be screened for HIV virus serology.

Diagnosis of Syphilis

Serological tests are the main diagnostic method in the diagnosis of syphilis. Treponemal tests and non-treponemal tests are used as serological tests. Both tests can be used initially as screening tests. It is confirmed by a non-treponemal antibody test followed by the more specific treponemal test. In the presence of clinical suspicion, the diagnosis of syphilis is made after the two tests are found to be reactive. More than a single test is required for diagnosis. However, both tests have limitations. For

Non-treponemal Tests	Treponemal Tests
Venereal Disease Research Laboratory (VDRL)	T. pallidum hemaglutinasyon testi (TPHA)
Rapid Plasma Reagin (RPR)	Microhemagglutination Assay T.pallidum (MHA-TP)
Toluidine Red Unheated Serum Test (TRUST)	Fluorescent treponemal antibody absorption (FTA-ABS)
	T. pallidumenzymeimmunoassay (TP-EIA)

example, non-treponemal tests may be positive in rheumatological diseases (e.g. SLE) [2].

Treatment for Syphilis

A single dose of benzathine penicillin G (2.4 million units intramuscularly) is standard therapy for primary, secondary, and early latent syphilis. Doxycycline, tetracycline, and ceftriaxone are alternative treatment agents [1].

Syphilis Aortitis

Frequency data for cardiovascular involvement in patients with untreated syphilis were obtained from two major studies: the Oslo study and the controversial Tuskegee study. The Oslo study first analyzed native Oslo patients hospitalized for primary syphilis from 1890 to 1910 and followed for 40-60 years. Cardiovascular syphilis (with or without saccular thoracic aortic aneurysm, aortic regurgitation, or coronary ostial stenosis) was diagnosed in 45 (15%) of 303 men and 47 (8%) of 584 women.

Tuskegee study began in 1932 and continued until 1972. It included 408 African-American men hospitalized for primary syphilis. Patients included in the study were followed without treatment with penicillin, which was introduced in the United States in 1943. The study subsequently caused great ethical debates. In 1952, approximately 1/3 of the patients died and 89 had autopsy findings. Fusiform aneurysm of the thoracic aorta was detected in 40 patients (45%), saccular aneurysm of the thoracic aorta in 7 patients (8%), and aortitis (by histological examination) in 41 patients (46%). Of the 89 patients examined at autopsy, 60 (67%) had positive serological test findings for syphilis when last tested; suspicious test results were found in 3 and negative results in 24. The clinical diagnosis of cardiovascular syphilis was made at autopsy in 88% of the patients (3). Of the 69 hearts (with existing weights), 48 (70%) weighed >400 g.

Syphilis aortitis manifests clinically 10-40 years after primary syphilis as aortic regurgitation, coronary ostial stenosis, or aortic aneurysm. In the pre-antibiotic era, up to 10% of untreated syphilis patients developed symptomatic cardiovascular complications, but nowadays the late form of syphilis is rarely seen in developed countries. Aortic regurgitation due to direct syphilitic involvement of the aortic valve or dilatation of the aortic ring affects 20-30% of patients with syphilitic aortitis. It is reported that 20-26% of the patients have coronary ostial stenosis. Although ostial involvement can cause symptoms of angina, it rarely results in myocardial infarction, as the slow process of stenosis allows the formation of collateral vessels. The prevalence of coronary ostium lesions with aortic regurgitation in patients with syphilitic aortitis has been reported as 14%. Aortic aneurysms are clinically detected in only 5-10% of patients, and 50% are seen in the ascending aorta [4].CT, MRI, and echocardiography are diagnostic imaging modalities used in aortitis. The specificity of CT scans for syphilitic aortitis has not been defined [5].

It is important to differentiate the involvement of the aorta from atherosclerosis. While the media and adventitia layer of the vessel is normal in atherosclerosis, fibrosis and inflammatory cells are seen in the media and adventitia layer in syphilis, and the vessel wall is thickened. The thickening results from extensive scarring of the adventitia and less dense fibrous tissue in the intima with or without calcium. The media layer is not thickened and thinner than normal, elastic fibers and smooth muscle cells may be completely absent in scar areas with fibrous tissue. Therefore, despite the thickening, the associated arterial wall is weaker than normal due to the disruption of the media's elastic fibers and smooth muscle cells. While widespread involvement is observed in syphilis, focal vessel involvement is observed in atherosclerosis, except for familial hyperlipidemia patients. The syphilitic process appears to involve only arteries with vasa vasorum. Vasa vasorum is found in the entire thoracic aorta but not in the abdominal aorta, and their absence in this part of the aorta seems to explain the absence of syphilitic involvement in the abdominal aorta [3].

If syphilitic aneurysms are not treated, the 2-year mortality rate is more than 80%. Obliterative endarteritis of vasa vasorum leads to an intense inflammatory reaction that may result in rupture of the aorta or fistulization to adjacent structures [6]. Antimicrobial pharmacotherapy and surgical treatment are recommended for the treatment of syphilis aortitis.

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INVITED REVIEWS

Single organ vasculitis: Description based on Chapel Hill Conference Consensus 2012 and a case report

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Definition

The term systemic vasculitis denotes the inflammation of blood vessels involving multiple territories or organs. Less often, vascular inflammation is restricted to a single organ, in which lesions may be focal or diffuse.

Single-organ vasculitis (SOV) is defined as vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of systemic vasculitis. Vasculitis distribution may be unifocal or multifocal (diffuse) within an organ. If the features of vasculitis are confined to one organ indicating that it is a limited presentation of systemic vasculitis, then it should be considered a limited presentation of that vasculitis, rather than SOV [1].

Clinical Features

a. Single-organ vasculitis with diffuse involvement

Diffuse SOV has been reported to affect the skin, central nervous system (CNS), kidneys, and coronary and pulmonary vessels. Diffuse SOV cannot be surgically treated and requires immunosuppressive treatment. Therefore, diffuse forms of SOV have higher relapse rates and a less favorable prognosis than focal SOV.

Primary CNS vasculitis (PCNSV) is one of the most recognized forms of SOV which can affect patients of any age. The symptoms are generally nonspecific, the patients may present with headache, stroke, or cognitive disorders [2]. It is important to rule out the conditions that may mimic PCNSV, including infections (e.g. tuberculosis, varicella-zoster virus), atherosclerosis, reversible cerebral vasoconstriction syndrome, and systemic rheumatological diseases. The diagnosis may be difficult because of the absence of a serological biomarker, the high false-negative rate of brain biopsy, and the angiographic findings that can be observed in other diseases. A complete analysis of cerebrospinal fluid should be done to rule out certain infections. Magnetic resonance imaging is useful in distinguishing PCNSV from reversible cerebral vasoconstriction syndrome [3].

Peripheral nervous system vasculitis, or *non-systemic vasculitic neuropathy (NSVN),* is usually presented clinically as distal axonal asymmetric progressive neuropathy, predominantly affecting the lower limbs. The Peripheral Nerve Society has published guidelines for the classification and treatment of NSVN. Although the sensitivity of the sural nerve and superficial peroneal nerve biopsies is low, it is emphasized that histopathological confirmation is important for diagnosis [4]. Also, ANCA tests should be negative and no histological evidence of vasculitis in a tissue other than nerves (with the exception of muscle involvement) should be present for the diagnosis of NSVC.

Localized vasculitis restricted to calf muscles is usually due to a local non-granulomatous vasculitis with necrosis and leukocytoclasis. The characteristic presenting symptoms are muscle pain, tenderness,

and swelling usually affecting a single calf muscle. Musculoskeletal and constitutional symptoms may also present in up to half of the patients. Concomitant skin lesions like purpura are also reported and this should be considered as a form of systemic vasculitis [5,6].The differential diagnosis includes popliteal cysts, deep vein thrombosis, and myositis.

Renal-limited vasculitis can occur without evidence of systemic disease. Weidner et al. compared the patients with renal-limited vasculitis with ANCA-associated vasculitis (AAV) with renal involvement. They reported that end-stage renal disease (ESRD) only occurred in 1 of 20 patients with renal-limited vasculitis, whereas nearly 30% of AAV patients progressed to ESRD. Despite the limited number of patients, the prognosis of renal-limited vasculitis seems better than AAV with renal involvement [7].

Isolated coronary or pulmonary arteritis is rare and is usually found incidentally after surgery or autopsy examination. Pulmonary artery SOV is also called isolated pulmonary Takayasu arteritis and imaging studies show an occlusive or stenotic pulmonary lesion in the majority of patients with the presence of high acute-phase reactants. It is reported that although some patients have a good outcome after surgery, there is a high risk for pulmonary hypertension postoperatively. A careful follow-up of these patients is mandatory because of the risk of vasculitis that can be seen in other vessels.

b. Focal single-organ vasculitis

Focal SOV may involve the breasts, genitourinary and gastrointestinal structures and is generally incidentally diagnosed after biopsy or surgical resection with the suspicion of cancer, infection or other abnormalities. Focal SOV has a very low risk of progression to systemic vasculitis. Most patients with focal forms of SOV can be cured after surgical resection of the affected tissue

Vasculitis of the breast is a rare condition that is characterized by non-granulomatous medium-sized vessel vasculitis which can occur bilaterally [8]. Granulomatosis with polyangiitis is the most common systemic vasculitis that presents with breast involvement [9]. The systemic vasculitides with breast involvement are generally present with constitutional symptoms, anemia and higher acute phase reactants, which are not present in the localized form [8]. It is also very important to rule out malignancy in a suspected case of vasculitis of the breast.

Vasculitis of urogenital structures is a rare condition that is reported at very low rates in gynecological and testicular surgeries [10,11]. In gynecological organ vasculitis, mostly small and medium-sized vessels are affected with a non-granulomatous vasculitis in contrast to systemic vasculitis with gynecological organ involvement, in which the most common histological finding is arteritis with giant cells. The most common symptoms are vaginal bleeding, pelvic pain, asymptomatic abdominal masses and uterine prolapse. In a review of 163 cases with gynecological organ vasculitis, it was reported that constitutional symptoms, anemia and high ESR are more common in systemic vasculitis when compared to SOV.

Testicular vasculitis typically presents with painful testicular and epididymal masses or swelling, and less commonly as a painless testicular or epididymal mass, which is unilateral in 80% of the cases. A non-granulomatous inflammation in medium-sized vessels is most commonly seen and coexistent malignancy is reported in some cases [11]. It was reported that the patients with systemic vasculitis and testicular involvement had more constitutional and musculoskeletal symptoms, anemia, and higher acute phase reactants when compared to isolated testicular vasculitis [11]. Polyarteritis nodosa is the most common systemic vasculitis with testicular involvement. Testicular involvement may also be seen in IgA vasculitis, Behçet's disease, Hepatitis-associated vasculitis, and ANCA-associated vasculitis, so a patient presenting with testicular vasculitis must be carefully investigated for these diseases.

Vasculitis of the gastrointestinal tract is extremely rare and it is often an incidental pathological finding of a biopsy of an abdominal mass or it may present as unexplained abdominal pain/ gastrointestinal bleeding [12]. Esophagus, stomach, small or large bowel, peritoneum, appendix, gallbladder, and pancreas can be affected. In a case series, 18 patients with vasculitis of the gastrointestinal tract were evaluated and the most common symptom was abdominal pain. The development of systemic vasculitis is most commonly seen in the first 5 months after the diagnosis [13]. In this regard,

because the vasculitis of the gastrointestinal tract may be the initial manifestation of systemic vasculitis, a complete evaluation of the patients for the presence of systemic vasculitis is required. The isolated vasculitis of the appendix and gallbladder can be cured after surgical excision and therefore has a good prognosis [14,15].

Diagnosis

Focal SOV is generally diagnosed incidentally and is a result of a biopsy or surgical resection done with the suspicion of cancer, infection or other abnormalities. Systemic vasculitis may affect all the regions in which SOV has been found to occur and isolated SOV may sometimes progress to systemic vasculitis. The diagnosis of SOV is less certain than any kind of systemic vasculitis given the uncertainty regarding future changes in disease patterns, therefore it is a 'working diagnosis' and may change to a systemic vasculitis in the follow-up.

A detailed questioning of symptoms and signs regarding systemic vasculitides and a careful physical examination should be done on all patients. According to the involved organ, multiple laboratory or imaging tests may be required to rule out infections, underlying malignancies and systemic vasculitis. A diagnosis of SOV can be done when there is no feature indicating systemic vasculitis and the other possible etiologies are excluded.

CASE PRESENTATION

A 32-year-old male presented with malaise, fever, swelling, and pain in the right scrotum in 2015. Ciprofloxacin was prescribed for a preliminary diagnosis of orchitis. Recurrent scrotal swelling and pain complaints without fever continued for four months and intermittent antibiotic therapy was prescribed. Scrotal Doppler ultrasonography was performed due to refractory symptoms. Oedema and increased thickness of the cutaneous and subcutaneous layers in the right scrotum, increased diameter of the right spermatic cord, and oedema in the wall, together with increased vascularity, inflamed, oedematous adipose tissue areas surrounding the vascular structures in the epididymis were detected. Right inguinal orchiectomy was performed with the preliminary diagnosis of chronic epididymo-orchitis. In pathological examination, necrotizing vasculitis in medium and small vessels, eosinophile-rich perivascular inflammation, and patchy involvement in adipose tissue, spermatic cord and testicular parenchyma adjacent to the epididymis were detected. He was referred to our rheumatology clinic for treatment and follow-up with the diagnosis of vasculitis.

The patient's past medical history did not reveal any chronic disease or use of regular medications. He had been smoking for five years. He did not have any systemic or organ-specific complaints other than fatigue and inflammatory arthralgia in the wrist, ankle, and knees for a month. Initial vital signs were fully normal. There was no abnormality in his physical examination. There was no abnormal result in laboratory results except for erythrocyte sedimentation rate (76 mm/hr) and CRP (55 mg/L) elevation. Anti-nuclear antibody, antibodies to extractable nuclear antigens, rheumatoid factor, antineutrophil cytoplasmic antibodies, viral serology, QuantiFERON-TB test and pathergy test were negative. Echocardiographic and electromyographic findings were normal. Computed tomography did not reveal any pathological image except a 4 mm nodule in the lung.

Although there were no signs of systemic vasculitis and the patient was diagnosed with isolated testicular vasculitis, because of the past musculoskeletal complaints and persistently elevated acute phase reactants, methylprednisolone 32 mg per oral daily and azathioprine 100 mg per oral daily treatments were initiated. Methylprednisolone was tapered and discontinued and azathioprine treatment was continued due to the absence of symptoms and normal acute phase reactants in the 6th month of treatment. Azathioprine dose was reduced to 50 mg after 5 years without a relapse, and the patient had no complaints and had normal acute phase reactants at the last visit.

Key messages

- Single-organ vasculitis (SOV) is vasculitis in an organ without the features of systemic vasculitis.
- Surgical excision is usually curative for focal SOV and it has a good prognosis.
- Diffuse SOV has a higher relapse rate and a less favorable prognosis than focal SOV.

– Immunosuppressive (IS) treatment is generally required for diffuse SOV, whereas only some cases of focal SOV may need according to the risk of relapse and damage in the involved organ.

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INVITED REVIEWS

HCV-related cryoglobulinemic vasculitis/Cryoglobulinemic vasculitis: Definition based on Chapel Hill Conference Consensus 2012 and case report

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Definition: Cryoglobulins are immunoglobulins that form precipitate at low temperatures and causing turbidity in the tube, and solubilise when the temperature is raised again to 37°C [1]. Detection of cryoglobulins in serum is called cryoglobulinemia. The formation of cryoglobulins is usually associated with an underlying disease [2]. The structure of the synthesized cryoglobulin varies depending on the underlying disease.

Three different subtypes were first defined by Brout et al. in 1974 according to their structure [3]. Type I Cryoglobulins are characterised by a monoclonal increase of a single immunoglobulin type, usually immunoglobulin M (IgM), less frequently IgG and rarely IgA. Bence Jones proteinuria can be detected because of mild chain loss in the urine. 10-15% of all cryoglobulinemias are type I [2]. Type II Cryoglobulins (Mixed Cryoglobulinemia); polyclonal IgG increase, light chain kappa or lambda structure, and monoclonal IgM increase against them (rheumatoid factor (RF) activity). 50-60% of cryoglobulinemias are type II. Type III Cryoglobulins (Mixed Cryoglobulinemia); Polyclonal IgM and IgG structure. 25-30% of cryoglobulinemias are type III [3]. It is important to obtain blood sample under appropriate conditions for cryoglobulinemia. There are several points to consider when detecting cryoglobulins. 10-20 ml of blood should be collected in an anticoagulant-free collection tube or syringe preheated to 37 °C. The sample should be transferred at ≥ 37 °C. Allow to clot for 1 hour at 37 °C. Centrifuge the collected serum at 37 °C. After centrifugation, the clot is removed with a Pasteur pipette and the serum is divided into 3 tubes. The centrifuged serum should be refrigerated (4 °C). If there is a precipitate, it should be re-solubilised at 37°C. Wash 3 times with isotonic at 4°C and centrifuge again at 4°C and solubilise again at 37°C for qualitative and quantitative examinations. Immunofixation electrophoresis, immunoglobulin levels and light chain (κ and λ) analysis are performed to typify the immunoglobulins in the cryoprecipitate [4,5].

Cryoglobulinemic vasculitis: The clinical importance of cryoglobulins has been recognized with the discovery of their association with purpura, arthralgia, renal failure and asthenia [6]. Cryoglobulinemic vasculitis, a disease that occurs in the presence of symptoms associated with the presence of cryoglobulins in serum. It is classified as immune complex-associated small vessel vasculitis according to the Chapel Hill consensus criteria [7].

Epidemiology: The prevalence of cryoglobulinemic vasculitis is rare and is approximately 1/100.000. It is usually observed between 45-65 years of age. The geographical distribution is variable. It is more common in southern Europe, where the endemic prevalence of hepatitis C virus (HCV)is higher, than in northern Europe. The female-to-male ratio is approximately 2-3/1 [8].

Etiology:

Type I: monoclonal - B-cell lymphoproliferative disorders:

– MGUS (monoclonal gammopathy of unknown significance) (50%), Multiple Myeloma, Waldenström's Macroglobulinemia, Non-Hodgkin's Lymphoma, Chronic lymphocytic leukemia, Castelman's disease

Type 2-3 (Mixed): Infectious and Non-infectious mixed:

– Essential (idiopathic) mixed type (48%)
– Infectious causes: Hepatitis B virus (HBV), HCV, etc.
– Connective tissue diseases [9].

Classification Criteria for Cryoglobulinemic Vasculitis

1. Subjective symptoms: Have you ever had one or more small red rashes on the skin, especially on the legs, have you ever had a red rash on the lower extremities that healed with brown scars, have you ever been told by a doctor that you have viral hepatitis?
2. Objective symptoms: constitutional symptoms (fever, fatigue, myalgia), joint involvement (arthralgia, arthritis), vascular involvement (purpura, skin ulcers, necrotizing vasculitis, hyperviscosity syndrome, Raynaud's phenomenon), neurological involvement (peripheral neuropathy, cranial nerve involvement, CNS involvement)
3. Laboratory abnormalities: Low C4 level, RF positivity, positive serum M component.

Cryoglobulinemia is classified as cryoglobulinemia when at least two of the findings summarised under the three headings are positive in a patient who has been cryoglobulin positive at least twice within a 12-week interval.

Clinical features: The majority of patients with cryoglobulinemia are asymptomatic and 2-50% may become symptomatic. The triad of purpura, arthralgia and malaise is present in more than 90% of patients. Hyperviscosity syndrome may be seen rarely in mixed cryoglobulinemias with a rate of <3% [10]. Clinical findings that may be observed less frequentlyinclude leg hyperpigmentation, Raynaud's phenomenon, leg ulcers, arterial hypertension, glomerulonephritis, hemorrhagic alveolitis, interstitial lung fibrosis, gastointestinal vasculitis, peripheral neuropathy, heart failure [11]. Factors associated with poor prognosis: pulmonary involvement, glomerular filtration rate (GFR) <60 ml/min, gastrointestinal involvement, age > 65 years [12].

Diagnosis: The diagnosis of cryoglobulinemic vasculitis begins with a detailed history and physical examination[13].TheItalianCryoglobulinemiaStudy Group (GISC) established a validated classification system for clinical trials and epidemiological purposes in 2014. These classification criteria are important for epidemiological studies due to their high specificity, but are not used for diagnosis [14]. The history should include constitutional symptoms (fever, weight loss, weakness, fatigue), arthralgia, myalgia, arthritis, rash and history of infection.Physical examination, should look for petechiae, purpura, livedo reticularis, skin ulcers, arthritis, neuromuscular findings (sensory neuropathy, clubfoot, etc.). In addition to laboratory tests (high RF, low C4, high AFR, microscopic urinary hematuria, proteinuria, hepatitis serology), it is important to detect cryoglobulins in the serum [15]. Investigation of monoclonal proteins, autoantibodies, tissue biopsy in selected patients, EMG and imaging studies are also helpful in the diagnosis. The diagnosis is usually made by the presence of typical symptoms (rash, arthralgia, myalgia, fatigue) and the detection of cryoglobulins in serum [16]. It is important to exclude differential diagnoses and to investigate other underlying diseases.

Differential Diagnosis: In the differential diagnosis, other autoimmune diseases, neoplastic diseases and other vasculitides should be kept in mind. Clinical findings may be similar to other vasculitides affecting small or medium-sized vessels. Sjögren's syndrome also shares common laboratory and clinical findings [17]. Positive Hepatitis C serology, the presence of autoantibodies and a low C4 level may be useful in the differential diagnosis. Erosive, symmetrical polyarthritis may develop in HCV-associated cryoglobulinemia. Similar to rheumatoid arthritis, RF elevation may also be observed. Anti-CCP antibodies are helpful in differential diagnosis [18].

Treatment: In type II/III cryoglobulinemias, the goal is to remove existing cryoglobulins from the circulation, suppress new cryoglobulin production and treat the underlying disease (autoimmune or viral disease) that triggers it. In non-severe involvement in mixed cryoglobulinemias, treatment is in the form of treatment of the underlying disease. In essential mixed cryoglobulinemias, low dose corticosteroids may be the first treatment option. Immunosuppressive and biologic agents are used to suppress B cells, antivirals are used to treat underlying chronic viral diseases such as HCV/HBV, and plasma exchange is used to remove cryoglobulins in the circulation [13].

CASE PRESENTATION

A 54-year-old male patient with no previous history of any medical conditionpresented with a rash on his legs. His history included, rash on the legs, swelling in the ankles, pain, difficulty in walking for the last 3-4 days,. Rheumatologic system questioning revealed weakness, fatigue, arthralgia, myalgia and rash. On physical examination, fever was 38.1 °C, liver was 2-3 cm palpable below the costae. Bilateral ankles are swollen and tender. There were Petechial-purpuric rashes on the lower extremities. Blood tests revealed high RF (363 IU/l), sedimentation (33 mm/h) and CRP (15.4 mg/dl). Blood tests revealed leukocyte 5280/mm3, hemoglobin 10.6 gr/dl, ANA 1/100 granular, Anti ds DNA negative, ANCA profile negative, Brucella agglutination, CMV, parvovirus PCR negative. C3: 42.6 (79-152), C4: 3.3 (16-38), Anti HCV positive, HCV RNA 2773 copies /ml, Cryoglobulin positive. In radiographic findings, liver size was 170 mm and spleen size was 150 mm in abdominal USG. There was no valvular pathology or vegetation in Echocardiography. İmaging studies showed no findings suggestive of infection or malignancy in. Based on theerse findings, The patient was diagnosed as cryoglobulinemic vasculitis.Ribavirin, roferon-A, prednisolone 30mg/day were started. Significant improvement was observed in his complaints. At the 12th month of follow-up, he presented with difficulty in stepping on his right foot. Physical examination revealed dorsiflexion weakness in the right ankle and big toe. EMG revealed decreased right peroneal superficial nerve conduction velocity. Cranial MRI and lumbar MRI showed no pathology. The patient was treated with pulse (1 g/day methylprednisolone) and rituximab 1000 mg (on days 0 and 15. every 6 months) with the diagnosis of low foot. Rituximab treatment was continued for 2 years. At the end of 2 years, the low foot improved. In blood tests, HCV RNA was negative, acute phase reactant, C3, C4, RF levels were normal. There were no signs of disease activation during follow-up.

Key messages

- Cryoglobulins are immunoglobulins that can precipitate at low temperatures and are responsible for the clinical picture of cryoglobulinemic vasculitis.
- The underlying disease is usually responsible for the synthesis of cryoglobulins.
- It is classified as small vessel vasculitis and shares clinical findings with other small vessel vasculitides. The detection of cryoglobulins in the serum is important in the differential diagnosis.
- The basis of treatment is to remove the cryoglobulins from circulation and to eliminate the disease that cause their synthesis.

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INVITED REVIEWS

Sarcoid vasculitis: Case presentation

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Definition

Sarcoidosis is a multisystemic disease of unknown etiology that affects many organs and is characterized by non-caseating granulomas (1). Vascular involvement of sarcoidosis is an extremely rare finding. In the terminology of vasculitides published by the Chapel Hill Conference in 2012, vasculitis associated with systemic sarcoidosis was defined as sarcoid vasculitis (2).

Clinical Features

Sarcoid vasculitis is a very rare vasculitis, and vasculitides involving small, medium and large vessels can be seen. In the literature, sarcoidosis-related leukocytoclastic vasculitides, polyarteritis nodosa-like vasculitides involving medium vessels, and Takayasu-like large vessel vasculitides have been reported (3). It is well known that patients with pulmonary sarcoidosis have signs of vasculitis involving vessels of all diameters, from large vessels to venules in the lungs (4). However, extrapulmonary vasculitis is not an expected finding very often(1).

The clinic in sarcoid vasculitis varies according to the type of vessel involved. In patients with small vessel involvement, skin involvement in the form of palpable purpura is prominent, while symptoms similar to Takayasu's arteritis may be seen in patients with large vessel involvement (such as limb claudication, dizziness, blood pressure difference, and murmur on the vessel).

Diagnosis

Radiological and histopathological findings in sarcoid vasculitis patients vary according to the type of vessel involved. Imaging is an important tool in diagnosis when large vessel involvement is present, and CT-angio, MR-angio or PET-CT can be used for this purpose. In patients with small vessel involvement, histopathological examination is essential, and biopsy is required from the affected area in suitable patients.

Case Report

A 52-year-old female patient applied to our clinic with complaints of pain in both arms and fatigue for 10 years. The patient had diagnoses of diabetes mellitus, hypertension, and sarcoidosis and smoked 60 packs/per year. The patient had been stented 5 years ago in the right brachiocephalic artery and right common carotid artery, and balloon angioplasty was performed on the right subclavian artery. Coronary angiography was performed 3 times in 5 years, and a stent was placed in the left main coronary artery, circumflex artery, and left anterior descending artery. A year ago, the patient was evaluated in the chest diseases outpatient clinic with dyspnea, cough, and weight loss. Thorax computer tomography (CT) revealed lymph nodes that increased in size in the right paratracheal, subcarinal, and right hilar regions. Fine-needle aspiration biopsy taken by endobronchial ultrasonography from the lymph

node, the largest of which is 20 mm in the right lower paratracheal area, resulted in granulomatous lymphadenitis. The patient was diagnosed with sarcoidosis and was followed up with symptomatic treatment. Four months after the diagnosis of sarcoidosis, echocardiography performed due to newly developed hypertension revealed a 50% ejection fraction and mild hypokinesia in the posterior apicoseptum. Coronary angiography was performed again in the patient, and 60-70% stenosis was detected in the stent in LAD and CX, but recanalization could not be achieved. The patient who applied to our clinic due to recurrent arterial thrombosis had normocytic anemia (Hb: 9 gr/dl, MCV: 85 fl) in her laboratory. Sedimentation and CRP were in the normal range; there was no hypercalcemia. Her ACE level was high (119 U/L), she did not have hyperlipidemia. The patient's previous CRP values were between 13 and 57 mg/L. In CT angiography, a stent was observed in the right common carotid artery and 85-90% stenosis was observed in the stent, fibrocalcific plaques causing approximately 75-80% field stenosis in the right carotid bulb, fibrocalcific plaques causing 75-80% field stenosis in the left carotid bulb. The stent lumen was open in the right brachiocephalic artery, and there were plaques in the proximal part of the right subclavian artery, causing approximately 80-85% stenosis. No stenosis was detected in the pulmonary artery branches and abdominal aorta branches of the patient. In PET CT, there were multiple lymph nodes with the largest 2,5 cm in the right supraclavicular, inferior jugular, along the right paratracheal chain, subcarinal area, bilateral hilar region (SUV max 12.6), no sign of large vessel vasculitis was detected.

Diffrential diagnosis

1. Giant cell arteritis
2. Atherosclerotic disease
3. Sarcoid vasculitis
4. Poliarteritis nodosa

In our case, existing vascular involvements were associated with sarcoid vasculitis, since the patient with a known diagnosis of sarcoidosis had recurrent medium-large vessel thrombosis and acute phase elevation accompanying these vascular events, the patient did not have hyperlipidemia, and there was no family history of cardiovascular disease at an early age. The large vessel involvement of the patient was thought to be related to sarcoidosis and a diagnosis of sarcoid vasculitis was made. Methotrexate 15 mg/week and prednisolone 10 mg/day were started.

Key messages

- Sarcoid vasculitis is an extremely rare disease.
- In sarcoid vasculitis, vessel involvement of any diameter can be seen.
- Before making a diagnosis of sarcoid vasculitis, other possible causes of vasculitis must be excluded. If possible, histopathological examination gives extremely valuable information in terms of diagnosis.
- In the treatment, immunosuppressive treatments are used together with steroids.

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