Received: 2019.08.28
Accepted: 2019.11.07
Published: 2020.01.14

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e919715
DOI: 10.12659/AJCR.919715

Multifocal Thrombophlebitis and Orbital Cellulitis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1,2 **Alojzija Hočevar**
BD 1 **Daša Šuput Skvarča**
ABDE 1,2 **Matija Tomšič**
BDEFG 1,2 **Katja Perdan Pirkmajer**

1 Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
2 Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Corresponding Author: Alojzija Hočevar, e-mail: alozjija.hocevar@gmail.com
Conflict of interest: None declared

Case series

Patients: Male, 76-year-old • Male, 73-year-old
Final Diagnosis: Multifocal thrombophlebitis and celulitis
Symptoms: Tender nodules
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Rare co-existence of disease or pathology
Background: Multifocal superficial thrombophlebitis is a rare clinical manifestation with wide differential diagnosis in relation to the background disease.
Case Report: Here we report on 2 patients who presented with a systemic inflammatory response, multifocal thrombophlebitis, and orbital inflammation in whom a diagnosis of a defined background disease could not be established.
Conclusions: The clinical pattern of our 2 cases might represent a distinctive, not yet defined systemic medical condition.

MeSH Keywords: Inflammation • Orbital Cellulitis • Thrombophlebitis

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/919715>

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Background

Multifocal migratory superficial thrombophlebitis is a relatively rare clinical manifestation and generally not an entity *per se*. The differential diagnosis is broad and includes malignancy (mainly as a paraneoplastic syndrome), infections (septic thrombophlebitis, human immunodeficiency virus, and syphilis), inflammatory bowel disease, Buerger Disease, and various hypercoagulable conditions [1–7]. Among primary systemic vasculitides, Behçet syndrome represents the most frequent vasculitis associated with vein inflammation, including superficial thrombophlebitis [8]. Only a few cases of idiopathic multifocal thrombophlebitis have been reported in the literature [9]. Cases of combined multifocal thrombophlebitis and orbital cellulitis have not been previously described.

Recently, we read with great interest the article from Watanabe et al., describing the case of episcleritis, thrombophlebitis, deep vein thrombosis, along with lung and central nervous system involvement, potentially representing a new vasculitic entity [10]. Herein we report 2 cases of multifocal superficial and deep thrombophlebitis, orbital cellulitis and episcleritis; cases to a degree similar to the one reported by Watanabe et al. Taken together, these 3 cases might indicate a unique vasculitic syndrome.

Case Reports

Case 1

A 76-year-old, previously healthy male, presented to our Rheumatologic Department in April 2017 with a 2-month history of fever (up to 39°C), weight loss (10 kg), dry cough, and multiple tender erythematous nodules on arms and legs, accompanied by high inflammatory activity [erythrocyte sedimentation rate (ESR) 110 mm/hour; C reactive protein (CRP) 76 mg/L (ref. 0–5 mg/L), procalcitonin 0.08 ug/L (ref. <0.5 ug/L), normocytic anemia (hemoglobin 97 g/L (ref. >130 g/L), hypoalbuminemia 23 g/L (ref. 36–45 g/L), polyclonal hypergammaglobulinemia

20 g/L (ref. 7–14 g/L), and ferritin 997 µg/L (ref. 20–300 µg/L)]. The patient had normal renal function and mild isolated microhematuria. He denied oral and genital ulcers, symptoms of inflammatory bowel disease, and was HLA-B51 negative (but HLA-B44 positive). An ultrasound of subcutaneous nodules demonstrated superficial thrombophlebitis with a thickened vein wall, vein thrombosis, and inflamed surrounding subcutaneous tissue (Figures 1, 2). An extended diagnostic procedure was performed, including a chest x-ray, abdominal ultrasound, positron emission tomography–computed tomography (PET-CT), a bone marrow biopsy, urine cytology, cystoscopy, gastroscopy, tumor markers [normal values of prostate-specific antigen (PSA), carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9), blood stool test (negative), immunoserological tests (antinuclear antibodies, antibodies against extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies (ANCA) were all negative], and widespread microbiological investigations [blood cultures, tests for tuberculosis, syphilis, Whipple disease, hepatitis, human immunodeficiency virus (HIV)], however, no firm background disease could be detected. On PET-CT an increased metabolic activity of the left subclavian vein was detected. There was no increased tracer uptake detected in large arteries. The biopsy of an enlarged inguinal lymph node seen on PET-CT showed reactive lymphadenitis. A biopsy of skin nodes was not performed. Since no evident cause of thrombophlebitis was found, the diagnosis of primary multifocal superficial thrombophlebitis was made, and after a failure of low molecular weight heparin to prevent new episodes of thrombophlebitis, a treatment with medium dose glucocorticoid (methylprednisolone 16 mg per day) was started with an immediate clinical and laboratory response. With the skin nodules and fever resolved, the inflammatory parameters decreased. In August 2017, a week after the discontinuation of steroids, the patient developed an episode of right eye episcleritis and orbital cellulitis. Glucocorticoids were reintroduced and again they controlled the disease successfully until December 2018, when an episode of right-side anterior uveitis developed. The uveitis was managed with local therapy. At the last follow-up visit in June 2019 the patient felt well and reported no episodes of thrombophlebitis

Figure 1. Superficial phlebitis (right lower leg, retromalleolar).

Figure 2. Superficial thrombophlebitis (right lower leg).

Figure 3. Superficial thrombophlebitis (on the left forearm).

or eye inflammation. During the 2-year follow up no associated disease to better clarify recurrent vein and ocular inflammation developed.

Case 2

Our second patient was a 73-year-old active smoker with a history of arterial hypertension, hyperlipidemia, and bladder papilloma, resected in 2015. The patient presented to our Rheumatological Department in August 2018 with a weight loss (10 kilograms in 4 months), low grade fever, fatigue, memory deficits, and a 1-month history of several episodes of tender nodules on the upper and lower extremities. He had raised inflammatory parameters (ESR 106 mm/hour, CRP 71 mg/L), hemoglobin 79 g/L, albumin 26 g/L, gamma globulins 13 g/L, ferritin 731 µg/L. He denied oral and genital aphthous lesions, bowel symptoms, chest and abdominal pain, and dyspnea at

admission. His renal function was normal and only minor urinary abnormalities were present (mild isolated microhematuria). The recurrence of papilloma was excluded with cystoscopy and urine cytology. Extensive immunoserological investigations (including ANCA and antiphospholipid antibodies) were negative. The patient was HLA-B51 positive. From the panel of the microbiologic test, an interferon-gamma (IFN-γ) release assay was positive. Active tuberculosis was subsequently excluded. A chest CT showed signs of emphysema and interstitial fibrosis (consistent with a nonspecific interstitial pneumonia pattern). A pulmonary function test revealed normal lung volumes, but the diffusion capacity for carbon monoxide was reduced (56% of reference). A bronchoscopy was performed and mixed cell alveolitis was found. An abdominal CT and esophagogastroduodenoscopy were not informative. An ultrasound of the skin nodules revealed phlebitis and superficial thrombophlebitis (Figure 3). Thrombophlebitis was found also at the right

Table 1. Comparison of clinical characteristics between cases.

Characteristics	Patient 1*	Patient 2#	Patient 3#
Age	67	76	73
Gender	Male	Male	Male
Race	Japanese	Caucasian	Caucasian
Smoking	NA	No	Yes
HLA B	39/44	44/44	07/51
Constitutional symptoms	Yes	Yes	Yes
Fever	Yes	Yes	Yes
Weight loss	NA	Yes	Yes
Superficial thrombophlebitis	Yes	Yes	Yes
DVT	Yes	No	Yes
Aphthous lesions	No	No	No
Skin involvement	Tender nodules	Tender nodules	Tender nodules
Headache	Yes	No	No
CNS involvement	Yes	No	No
Eye involvement	Episcleritis	Episcleritis, uveitis Orbital cellulitis	Orbital cellulitis
Lung involvement	Nodular lesions	No	NISP
Renal involvement	NA	No	No

* A case described by Watanabe et al.; # our 2 cases. DVT – deep vein thrombosis; CNS – central nervous system; NISP – nonspecific interstitial lung disease; NA – data not reported.

saphenofemoral junction. A neurologist confirmed mild cognitive impairment, consistent with cortical atrophy and old lacunar ischemic lesions found on the head CT. Despite a broad diagnostic workup, no firm diagnosis was made. Stemming from the experience of our previous patient and again the ineffectiveness of the prescribed anticoagulant therapy, we started treatment with glucocorticoids (methylprednisolone 48 mg per day) with good response. The skin lesions disappeared, and the inflammatory parameters decreased. In November, while still receiving 4 mg methylprednisolone daily, the patient presented with left orbital cellulitis of unknown etiology. The inflammation was resolved with a course of amoxicillin and clavulanic acid and local steroids. In April 2019, the cellulitis recurred in the right eye, accompanied by a new episode of limb superficial thrombophlebitis. This time steroid dose was increased (to 16 mg methylprednisolone per day) and azathioprine 100 mg per day was added to the regular therapy. Currently the patient is stable and no new signs/symptoms toward a defined background disease has developed.

Discussion

Our 2 cases of multifocal thrombophlebitis and orbital cellulitis resemble the case described recently by Watanabe et al. [10]. The Japanese group reported a case of unclassified vasculitis manifesting with episcleritis, thrombophlebitis, deep vein thrombosis, and lung and intracranial involvement. Likewise, our 2 patients presented with thrombophlebitis of superficial and deep veins, followed by orbital inflammation (Table 1). The limitation of our report is that a skin biopsy of the nodular lesions was not performed, but an ultrasonographic description of thrombophlebitis was convincing. The orbital cellulitis could not be etiologically defined despite the broad investigations. As the inflammation responded to steroids, it probably represented the same pathogenic process as prior nodular skin lesions. Similarly, as Watanabe et al., we suspected Behçet disease, but could not confirm it. Our first patient was HLA-B44 positive, like the Japanese patient. Our second patient harbored an HLA-B51 antigen; however, it is unlikely for Behçet disease to begin in the eighth decade of life, and without characteristics like recurrent oral or genital aphthae.

In addition, the prevalence of HLA-B51 in our population is around 14%, so the finding of HLA-B51 in our patient could be accidental. The disease of our 2 patients could neither be classified as ANCA associated vasculitis or any other known systemic vasculitis. To the best of our knowledge, we could classify the disease as a large to medium sized vein vasculitis. Despite extensive imaging and cytological investigations, we did not confirm any malignant disease in our patients, neither at presentation nor during follow up. Chronic active infection, including those associated with migratory thrombophlebitis in the literature, was excluded. As patient's manifestations also remain unclassified during follow up, one could speculate a distinct, not yet defined medical condition/entity [11,12]. We concur with Watanabe et al. that a new disease entity might exist, but more cases are needed to better define it.

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Conclusions

Here we report 2 cases of multifocal superficial and deep thrombophlebitis with subsequent orbital cellulitis. The clinical pattern of our 2 cases might represent a distinctive, not yet defined systemic medical condition.

Conflict of interest

None.