Vasculitis mimics caused by Pythium infection and literatures review

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Abstract

While early diagnosis of vasculitis is important to induce remission and prevent organ damage, an incorrect diagnosis can result in harmful consequences from missing the underlying condition and exposure to immunosuppressive therapy. Evaluation of vasculitis should include consideration of its mimics. Important mimic categories include infection, vasculopathy, non-inflammatory conditions like atherosclerosis, thrombotic states, calciphylaxis and rare neoplasms. Human pythiosis is a rare life-threatening disease caused by *Pythium insidiosum*, a fungus-like organism that belongs to the *Kingdom Straminiphila*. Infected patients were mostly reported from Thailand and usually had an agricultural background. Clinical presentations are documented, cutaneous/subcutaneous, ocular, vascular, and disseminated pythiosis. The majority of the reported patients with vascular pythiosis have lower limb involvement. Known risk factors for vascular pythiosis include thalassemia, hemoglobinopathy, paroxysmal nocturnal hemoglobinuria, aplastic anemia, and leukemia. Furthermore, the rarity of the disease has led to underrecognition, under-diagnosis, and delays in diagnosis, and this has contributed to the occurrence of advanced disease, which affects survival. I, herein, report a case of diabetes mellitus and alcoholism, 31 year-old male presented with ischemic leg ulcers, which skin biopsy revealed leukocytoclastic vasculitis and CT- angiogram suspected vasculitis, and then *P. insidiosum* has been isolated from vascular sites, and relevant literature reviews.

Keywords: Vasculitis mimics, *Pythium insidiosum*, vascular pythiosis

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The vasculitides encompass autoimmune conditions affecting the blood vessels and causing end-organ damage. The 2012 International Chapel Hill Consensus Conference provides definitions for the different forms of vasculitis and also a framework to categorize them. [(1)] In addition to large, medium, and small vessel vasculitis, other categories include variable vessel vasculitis, single-organ vasculitis, vasculitis with probable aetiology, and vasculitis associated with autoimmune diseases.[1]

Multiple conditions may mimic vasculitis.[2–8] While early diagnosis of vasculitis is important to induce remission and prevent organ damage, an incorrect diagnosis can result in harmful consequences from missing the underlying condition and exposure to immunosuppressive therapy. Evaluation of vasculitis should include consideration of its mimics. Medications and illicit drugs like cocaine can cause vasculitis and are important in identifying secondary causes. As in the case of vasculitis, an approach to mimics based on the anatomic size of vessels can be useful. Important mimic categories include infection, vasculopathy, non-inflammatory conditions like atherosclerosis, thrombotic states, calciphylaxis, and rare neoplasms. While infections can affect any vessel size, vasculopathies typically mimic large and medium vessel vasculitis. Cholesterol emboli, thrombotic and hypercoagulable conditions, and calciphylaxis are important mimics of medium and small vessel vasculitis. Neoplasms like cardiac myxomas can mimic vasculitis of any vessel size, while intravascular large cell lymphoma is an important mimic of primary angiitis of the CNS.[6-8]

Human pythiosis is a rare, life-threatening disease caused by *Pythium insidiosum* (*P. Insidiosum*), a fungus-like organism that belongs to the *Kingdom Straminiphila*.[9-10] Infected patients were mostly reported from Thailand and usually had an agricultural background. Clinical presentations are documented: cutaneous/subcutaneous, ocular, vascular, and disseminated pythiosis. The majority of the reported patients with vascular pythiosis have lower limb involvement. Known risk factors for vascular pythiosis include thalassemia, hemoglobinopathy, paroxysmal nocturnal hemoglobinuria, aplastic anemia, leukemia, myelodysplasia, idiopathic thrombocytopenic purpura, and, to a lesser extent, young age, alcoholism, malnourishment, immunosuppression, HIV infection, cancer, and neutropenia.[11-20]

Furthermore, the rarity of the disease has led to underrecognition, underdiagnosis, and delays in diagnosis, and this has contributed to the occurrence of advanced disease, which affects survival.[(12-17)] I, herein, report a case of a 31-year-old Thai male with poorly controlled diabetes mellitus and alcoholism, with ischemic leg ulcers, which skin biopsy revealed leukocytoclastic vasculitis, and Computerized tomography-angiogram (CT-A) suspected vasculitis, and then *P. insidiosum* has been isolated from vascular sites. For this case study, the patient gave written informed consent.

Case

A 31-year-old Thai man, general contract occupation, poorly controlled Diabetes mellitus and alcoholism, was admitted to the Provincial hospital due to low-grade fever and painful left leg ulcers for 14 days. He had not been exposed to a swampy area before the occurrence of leg lesions. Skin biopsy diagnosis was leukocytoclastic vasculitis (LCV). (Figure 1) Complete blood count (CBC) showed hematocrit 30%, white blood cell count (WBC) 5800 cells/µl, and platelet count 184,000 /µl . Erythrocyte sedimentation rate (ESR) was 18 mm/hr. Urine examination revealed albumin negative, RBC 0-1/OF. The chest film was an unremarkable study. Echocardiogram revealed LVEF 78%, no pulmonary hypertension, and normal valves. CT-A was done, and revealed total occlusion along the left proximal to distal anterior tibial artery, left plantar arch with mild diffused wall thickening and adjacent perivascular fat haziness, could be vasculitis. (Figure 2) Serologic studies; HBsAg, anti-HCV, anti-HIV, VDRL, TPHA, P-ANCA, C-ANCA, and ANA were all negative. He was commenced on various intravenous antibiotics and dexamethasone with no improvement. Due to his severe ischemic pain and new ulcers developed, he was referred to the Rheumatology clinic at Buddhachinaraj Hospital, after 47 days of admission.

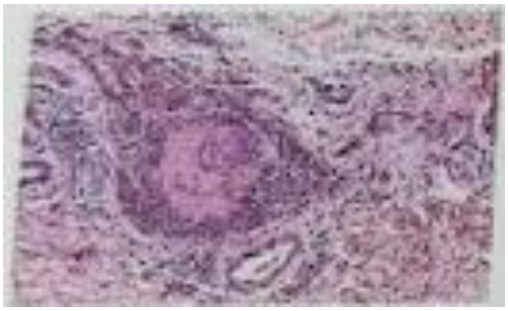

Figure 1 Skin biopsy; pertivascular inflammation comprised predominantly of neutrophils, debris, and extravasated RBC. Diagnosis: Leukocytoclastic vasculitis

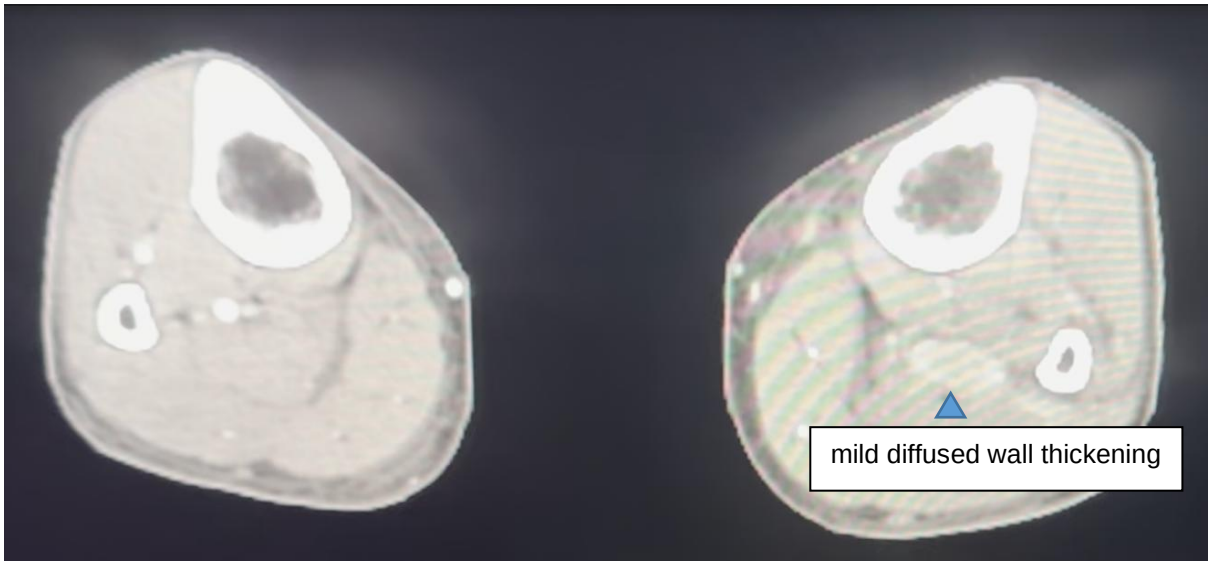

Figure 2 Initial CT-A revealed total occlusion along the left proximal to distal anterior tibial artery, left plantar arch with mild diffused wall thickening and adjacent perivascular fat haziness, which could be vasculitis.

His lesions when he was referred to Buddhachinaraj hospital are shown in Fig. 3. Physical examination revealed febrile, mild pallor and mild painful edema of his left legs. The left dorsalis pedis pulse was decreased. CBC showed hematocrit 34.5%, WBC16,470 cells/µl and platelet count 184,000 /µl. ESR was 18 mm/hr. Blood smear showed hypochromic 1+, microcytic 1+, and no fragmented red blood cells. Urine examination revealed albumin negative, RBC 0-1 /OF. Gram stain, acid fast stain, modified acid fast stain, and Wright's stain were performed on discharge of the leg ulcers and did not show any organisms. Anti-cardiolipin, anti-β2 glycoprotein, and lupus anticoagulant were all negative. Serum levels of protein and protein S were normal. The chest film was an unremarkable study. Emergency CT-A femoral run off revealed total occlusion of the distal left popliteal, anterior tibial, posterior tibial, and peroneal arteries. (Figure 4). Emergency left transpopliteal embolectomy with clot removal was performed. The pathology of the clot exhibited ribbon-like, pseudoseptation with right-angle branching fungus. The differential diagnosis of fungal hyphae was Pythiosis and Mucormycosis. (Figure 5). Human vascular pythiosis was diagnosed, and treatment was commenced with oral itraconazole, azithromycin, and doxycycline.

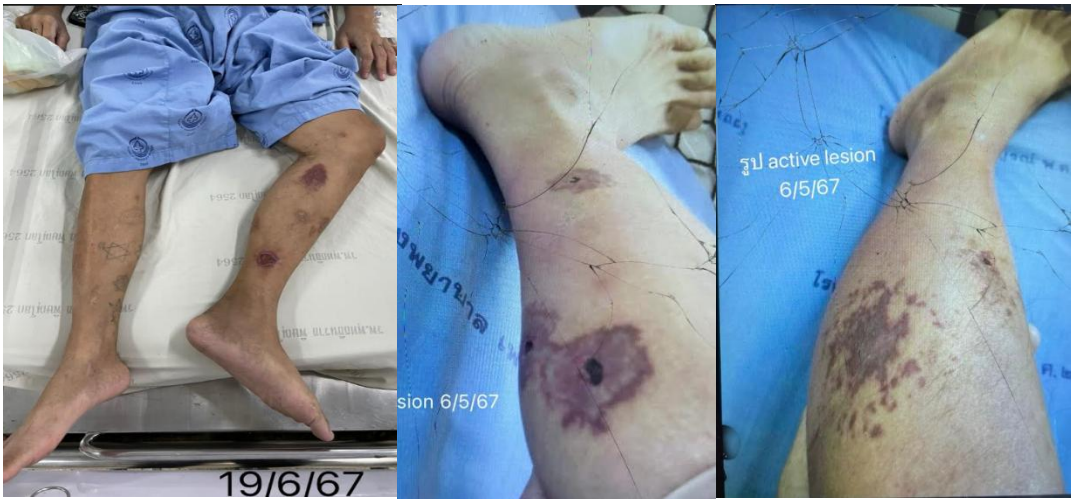

Figure 3 Chronic ulcer of both legs from Pythium insidiosum.

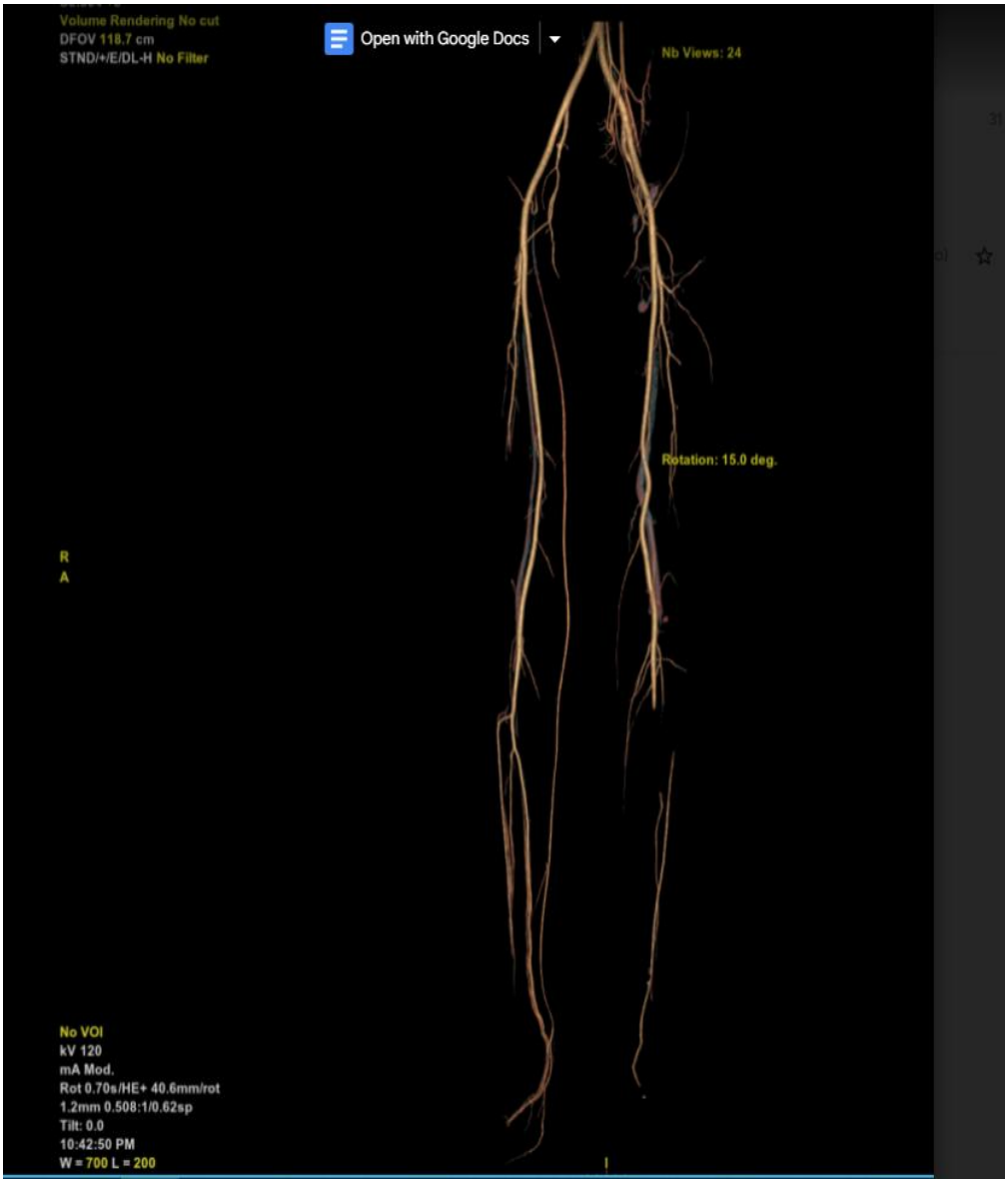

Figure 4 Emergency CT-A femoral run off revealed total occlusion of distal left popliteal, anterior tibial, posterior tibial, and peroneal arteries.

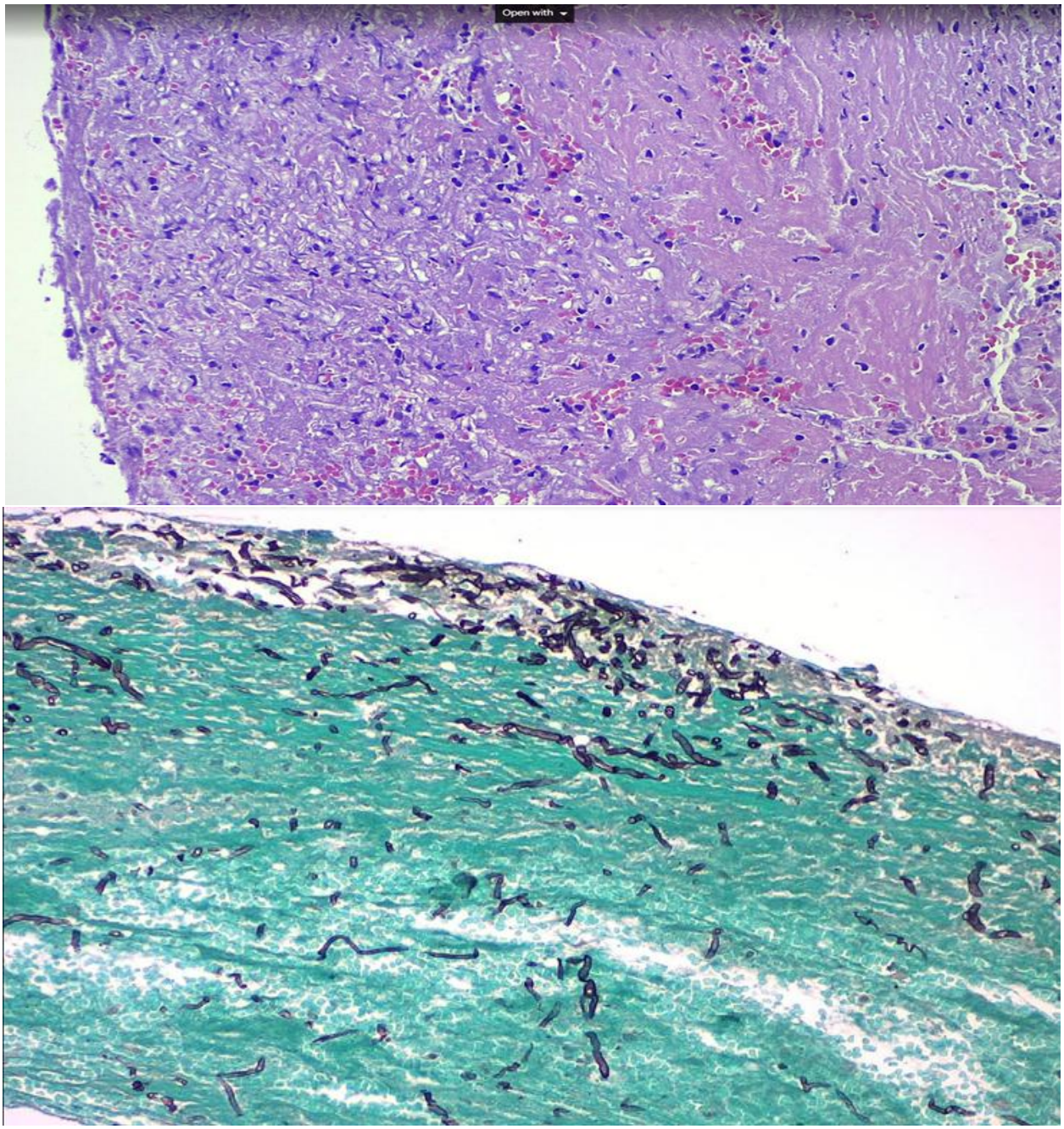

Figure 5. The pathology of the clot exhibited ribbon-like, pseudoseptation with right-angle branching fungus.

A psychiatrist and an Orthopedic surgeon were promptly consulted for left above-knee amputation. Unfortunately, he denied our procedure and requested referring back for conservative treatment after 17 days of admission. Hemoculture for fungus showed no growth. *P. insidiosum* antibody was positive. Three weeks later, on 31 July 2024, he came back to Buddhachinaraj hospital due to unbearable left leg pain, and left above-knee amputation was done immediately without repeating the CT-A. Antimicrobial drugs with oral itraconazole, azithromycin, and doxycycline were continued for six months. Three weeks later, at the outpatient department, his stump and surgical wound were completely dry and neat. Then he requested further medication at the nearby hospital. At the end of six months, I asked about symptoms over the phone and found that there were no new wounds, but phantom pain. Serum P. insidiosum antibody was not done.

Discussion

The suspicion for vasculitis should be high in the presence of a robust systemic inflammatory response and a high number of involved organs, and high laboratory markers of inflammation. The diagnosis of vasculitis requires a high index of suspicion, especially in the systemically unwell patient with multiorgan involvement. Symptoms and signs of vasculitis depend upon the vessels involved. Large vessel vasculitis typically presents with limb claudication, absent pulses, and unequal blood pressure, while small vessel vasculitis presents with palpable purpura and proteinuria. Medium vessel vasculitis, which involves the main visceral arteries and their initial branches, produces symptoms according to the involved vessels and the circulation.[1]

The CTA can detect pathological changes in large, deep vessels with a convenient scanning time and good spatial resolution. CT can assess the vessel wall and the lumen, and it can therefore show changes in the vessel wall that are not seen on conventional angiography. Abnormal radiography showing thickening of the vessel wall with enhancement, thrombosis, and aneurysmal dilation may indicate arteritis.[20] Arterial wall enhancement on CTA has been linked to disease activity in a few studies, however, other studies with differing results have been reported. The role of CTA in monitoring disease course has also been proposed, according to which there is a resolution in wall enhancement after successful treatment.[22] Arterial wall enhancement could be due to inflammation, infection, or cracked thrombotic plaque. Therefore, clinical correlation is absolutely necessary.

Subcutaneous form of pythiosis histopathology revealed a granulomatous reaction, diffuse infiltration, and oedema of the vessel walls.[9] That could mimic vasculitis.[11-20]

In this patient, due to skin biopsy, revealed LCV and he had medium sized arteries occlusion even though he had no previous oral/genital ulcer neither red eye, nevertheless Behcet's disease could be the aetiology, but his symptoms did not response to high dosage of dexamethasone, in addition to normal inflammatory marker (ESR) and involved only medium size arteries that can distinguish it from vasculitis. Important aetiologies that can mimic vasculitis are infections, vasculopathies, and other non-inflammatory conditions like atherosclerosis and thrombotic conditions. Rare aetiologies like myxoma and intravascular lymphoma should also be considered in certain circumstances. It is important to follow patients diagnosed with vasculitis over time and strongly reconsider mimics in patients treated for vasculitis who do not respond to immunosuppressive therapy. Recognition of the clinical presentation of the mimics, organs/ vessels that may be affected, and features that can distinguish it from vasculitis can help avoid the pitfalls of incorrectly mistaking a mimic for vasculitis.[11-20]

Pythiosis is caused by *P. insidiosum*, a species of the *Kingdom Stramenopila* that has been implicated in human and animal infections. It has been reported worldwide, especially from tropical, subtropical, and temperate areas. The first case of human pythiosis was reported from Thailand in 1985.[11,14] *P. insidiosum* presents in two forms: perpendicular branching hyphae and a biflagellate zoospore, which shares some morphological characteristics with fungal members of the order *Zygomycetes*. However, phylogenetic analysis shows that *Pythium* species are more closely related to diatoms and algae than true fungi.[10] Clinical presentations of human pythiosis can be classified into four types: cutaneous/ subcutaneous, vascular, ocular, and disseminated forms.[11-20] Cutaneous/ subcutaneous infection can lead to vascular and disseminated diseases. The majority of the patients affected with cutaneous, vascular, and disseminated forms have underlying thalassemia/ hemoglobinopathy syndrome, while a minority of them have underlying aplastic anemia, paroxysmal nocturnal hemoglobinuria. Ocular pythiosis is exceptional in that it can affect otherwise healthy individuals.[14-15] Vascular pythiosis had been reported only in Thailand[8-20,] and recently, one case (17-year-old man, severe aplastic anemia) was vascular pythiosis) in Jamaica,[23] all clinical presentations were ischemic necrosis of the lower extremity, but ocular pythiosis had been reported in various countries.[11-20]

This patient has poorly controlled diabetes mellitus and alcoholism, has vascular pythiosis, presented with painful ulcers along the left leg, and pain in the left leg without ischemic necrosis of his toe, which has never been reported.

Histopathology and angiography are not specific to diagnose pythiosis, as the morphology of the organism is similar to other fungi, such as mucormycosis and aspergillosis. Culture identification is a gold standard. Creamy white and glabrous colonies of *P. insidiosum* are usually detected after 24–48 h of incubation. However, it is a time-consuming method and requires expertise. Molecular diagnosis (PCR) and the serological assays (immunodiffusion and immunochromatographic tests) are therefore useful to make a diagnosis of human vascular and cutaneous pythiosis. It should be noted that false-negative results can occur in patients with ocular pythiosis.[10]

Regarding the management of vascular pythiosis, mortality was up to 100% in patients without complete surgical resection regardless of other adjunctive therapy prompt radical surgery leading to amputation to achieve pathogen-free surgical margin is the mainstay of successful treatment in combination with the administration of antifungal drugs and *P. insidiosum*-antigen (PIA) formulation, remain the recommended treatment.[11-19, 21-27]

Sermsathanasawadi et al suggested adequate resected proximal margin is 5 cm above the site of the arterial lesion detected by CTA.[27]

Amphotericin B and ketoconazole do not have therapeutic activity against *P. Insidiosum.* [(16)] A combination of terbinafine, itraconazole, and immunotherapy was developed in 1981. It was first successfully used to save a Thai boy with vascular pythiosis in 1998. Wanachiwanawin et al reported the efficacy of immunotherapy in eight patients with vascular pythiosis. [(14)] Four patients (50%) had dramatic and complete remission, while the other two (25%) showed partial response. The overall efficacy of immunotherapy in human, including the first case, is approximately 56%[14]

Antifungal drugs are generally ineffective against *P. Insidiosum*. In vitro, minimal inhibitory concentration (MIC) data revealed amphotericin B had the highest MIC, followed in order by voriconazole, fluconazole, anidulafungin, caspofungin, itraconazole, and terbinafine.[29]

The combination of itraconazole and terbinafine was commonly used, owing to its ability to synergistically inhibit growth in vitro. However, synergistic effects between itraconazole or voriconazole and terbinafine could not be demonstrated in Thai *P. insidiosum* isolates.[27]

In vitro susceptibility results, tetracyclines and macrolides had the most favorable MIC, and synergistic effects were observed in combinations of these two antibiotic classes. Adjunctive use of azithromycin and doxycycline preliminarily improved survival in vascular pythiosis patients with residual disease.[25]

The study from the King Chulalongkorn Memorial Hospital (KCMH) (2020), the pythiosis research group showed that Thai *P. insidiosum* isolates were susceptible to azithromycin and doxycycline. Hence, the antimicrobial regimens under the KCMH research protocols were transitioned to itraconazole plus azithromycin; subsequently, doxycycline was added to the treatment protocol due to evidence of a synergistic effect with azithromycin and doxycycline in combination against Thai *P. Insidiosum.*[25-26] Use of adjunct antimicrobials holds considerable promise in mitigating disease relapse. During treatment, clinical assessment of the vascular pythiosis patient should be performed daily.[(16,19,23)]

Immunotherapy demonstrated an acceptable safety profile, but the efficacy remains inconclusive due to the small sample size.[28,30]

Recently, Hanna Yolanda and Theerapong Krajaejun (2021) revealed that both immunotherapy, comprising CFA (extracellular antigens) and SABH (intracellular antigens), showed no significant differences in clinical outcomes for patients with vascular or ocular infection.[28]

Follow-up and monitoring of daily physical assessment of soft tissue, surgical sites, lymphadenopathy, and signs of vascular insufficiency are critical after surgery. Stump abscesses, and myositis along with evidence of arterial insufficiency syndrome arteritis, thrombosis, aneurysm, pulsatile mass) represents residual disease that necessitates investigation and aggressive management.[17-27]

Serum β-d-glucan and *P. insidiosum*-specific antibody are potential biomarkers of vascular pythiosis after treatment initiation.[29] Serum β-d-glucan declined three months after surgery and became undetectable among survivors. Persistently elevated serum β-d-glucan at two weeks after surgery should prompt an evaluation for residual disease. Dead patients had statistically significantly higher levels of serum β-d-glucan, compared with survivors.[31]

Conclusion

This 31-year-old Thai male, with poorly controlled diabetes mellitus and alcoholism, with ischemic leg ulcers, for which skin biopsy revealed leukocytoclastic vasculitis, and CT-A suspected vasculitis, and then *P. insidiosum* was isolated from vascular sites and positive *P.insidiosum* antibody, was (cutaneous/subcutaneous and vascular pythiosis) misdiagnosis as vasculitis. It is important to follow patients diagnosed with vasculitis over time and strongly reconsider mimics in patients treated for vasculitis who do not respond to immunosuppressive therapy. Recognition of the clinical presentation of the mimics, organs/vessels that may be affected, and features that can distinguish it from vasculitis can help avoid the pitfalls of incorrectly mistaking a mimic for vasculitis.

Appropriated treatment in Thai vascular pythiosis is adequate, resected proximal margin is 5 cm above the site of the arterial lesion detected by CTA, itraconazole, azithromycin, and doxycycline, which should be continued at least six months or until serum P. insidiosum is negative. Clinical assessment of the vascular pythiosis patient should be performed daily for surveillance of residual disease.

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