Vexas Syndrome Presenting As Long Covid-19

Vexas-Syndrom zeigt sich als Long Covid-19

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ABSTRACT

Objective VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently described systemic inflammatory syndrome caused by somatic mutations of UBA1. COVID-19 is a viral infection that was described in 2019 and spread widely and quickly all around the world. Constitutional, thrombotic and pulmonary symptoms of these two conditions are similar, which is why cases of VEXAS syndrome may be misdiagnosed as a COVID infection.

Case report We introduced a case report of a 72-year-old male patient with VEXAS syndrome who had fever, fatigue, deep vein thrombosis and a cough and was thought to have a long COVID-19 infection for one year. Then we diagnosed him with VEXAS syndrome with vacuoles in myelomonocytic cells, skin lesions and a mutation of the UBA-1 gene.

Conclusion VEXAS and long COVID are two new conditions with overlapping clinical presentations. Physicians must be aware of these clinical conditions because of their different treatment strategy and prognosis.

Introduction

VEXAS syndrome is characterized by fever, neutrophilic dermatosis, pulmonary infiltrates, thrombosis, hematologic abnormalities, vasculitis, chondritis and musculoskeletal complaints [1]. Due to wide spectrum of manifestations, a large proportion of VEXAS patients are misdiagnosed and treated as **large and medium vessel vasculitides**, malignancies, Still's disease, relapsing polychondritis, **Schnitzler syndrome**, hematologic conditions [2]. Coronavirus disease 2019 (COVID-19) is an acute inflammatory-thrombotic condition that might affect almost all organ systems [3]. **This clinical condition may interfere with bacterial and fungal infection, acute respiratory distress syndrome, acute pulmonary edema, chronic eosinophilic pneumonia** [4]. Persistent, prolonged, and often debilitating manifestations are increasingly recognized among COVID-19 convalescent individuals, even those who had asymptomatic illness, named 'long COVID syndrome' [5] with similar clinical symptomatology of VEXAS syndrome including fatigue, interstitial lung disease, skin lesions, myositis, arthritis, neurologic and cardiovascular manifestations ([5, 6] ▶ **Table 1**). Because of the similarities in both conditions, exacerbations of VEXAS syndrome may be mistaken as long COVID-19 which requires a different treatment approach. Herein, we presented a case of VEXAS

▶ **Table 1** Presenting manifestations of VEXAS and Long COVID syndromes.

	VEXAS	Long COVID
Constitutional	Fatigue, malaise, weight loss, fever	Fatigue, malaise, weight loss, fever, sweating
Respiratory	Alveolitis, pleural effusion	Cough, alveolitis and fibrosis
Cardiovascular	Venous and arterial thrombosis, vasculitis, aortitis, pericarditis, myocarditis,	Hypertension, palpitations, pericarditis, myocarditis, thromboembolism
Gastrointestinal	Diarrhea, abdominal pain	Ageusia, nausea, anorexia, sore throat, diarrhea, abdominal pain
Hematologic	Cytopenia, myelodysplasia, macrocytic anemia, lymphadenopathy, splenomegaly	Inflammation anemia, hemolytic anemia, thrombocytopenia
Neuropsychiatric	Peripheral neuropathy	Headache, insomnia, mood disturbance, cognitive dysfunction, peripheral neuropathy, Guillain-Barré syndrome, myelitis
Skin	Neutrophilic dermatitis, urticaria, erythema nodosum, chondritis	Alopecia, rash, nail alterations
Musculoskeletal	Myalgia, arthralgia, arthritis	Myalgia, arthralgia, arthritis
Eye	periorbital edema, scleritis, episcleritis, uveitis	Conjunctivitis

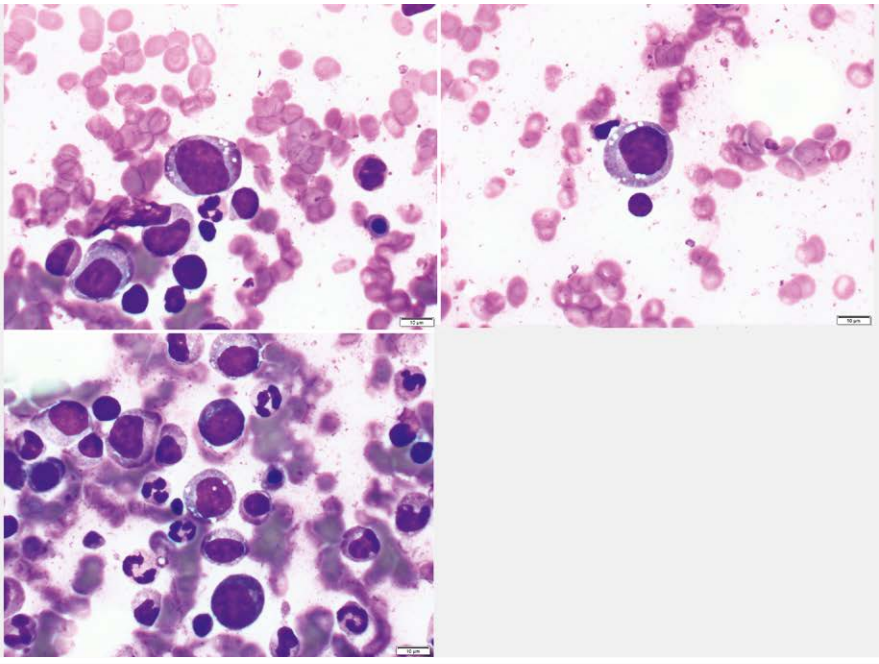
syndrome mistaken as long COVID and briefly discussed the similarities and differences between these two entities, finally giving potential clues to differentiate VEXAS from COVID-19.

Case Report

A 72-year-old man presented with the complaints of fever, fatigue, shortness of breath and cough for 20 days to the infectious diseases department in 2021. He gave a history of small rose-pink skin lesions on his trunk and upper arms which was diagnosed as Sweet syndrome four years before with the abundance of neutrophils and nuclear debris in his skin biopsy. (▶ **Fig. 1**) He gave an anamnesis of hospitalisation with a positive SARS-CoV-2 rtPCR and consistent pulmonary infiltrates on thorax computed tomography in an intensive care unit one year before. He discharged from hospital with complete recovery of respiratory symptoms, lingering musculoskeletal complaints, and significant weight loss. He had recurrent brief hospitalizations three times in a year due to fever, dyspnea, cough and severe fatigue, and he was treated with short courses of corticosteroids and antibiotics with a partial response with a diagnosis of long COVID. On his previous hospitalization thorax and abdomen CT revealed pulmonary thromboembolism and occlusion of left femoral artery and also paratracheal, bilateral hilar, subcarinal lymphadenopathies. Therefore, he was anticoagulated with warfarin. His past medical history was otherwise unremarkable. On his admission to our hospital, he seemed cachectic and lethargic, and confined to bed. His fever was 38,3°C and respiratory rate was 28 bpm. He had warm, swollen and tender left wrist and right knee as well as significant limb muscle tenderness. A few millimetric non-tender erythematous papules were noted all over his neck, trunk, and arms. Laboratory examination revealed leukocytosis (WBC 4112/mm^3, neutrophil 3200/mm^3, lymphocyte 490/mm^3) and macrocytic anemia (Hemoglobin 8,8 gr/dL, MCV110.fL). Other pertinent laboratory parameters were as follows LDH: 209 U/L, AST: 15 U/L, ALT: 11 U/L, creatinine: 0,49 mg/dL, ferritin: 480 ng/mL, CRP 87,5 mg/L (N < 5) and ESR 117 mm/h. Because of suspicion for myelodysplastic syndrome, a bone marrow biopsy was performed which showed notable hypercellularity and vacuolated myelomonocytic precursors (▶ **Fig. 2**) with normal karyotype and microarray results. Genomic sequencing revealed a somatic mutation in UBA1 (NM_003334.4) c.121 A[C (p.Met41Leu). He was subsequently diagnosed with VEXAS syndrome and treated with 60 mg/day prednisolone with a dramatic amelioration of complaints and normalization of acute phase reactants. His symptoms relapsed when the prednisone dose was lowered to 20 mg day. He was doing well on his last visit two months before while he was receiving 30 mg prednisone and under consideration for alternative treatment modalities.

▶ **Fig. 1** Skin lesions diagnosed as Sweet syndrome.

VEXAS syndrome is associated with somatic mutations affecting UBA1 which is located on X chromosome, therefore most of the affected are male elderly patients [1, 2]. UBA1 encodes the major E1-activating enzyme responsible for activation of all cellular ubiquitin signaling and mutations result in decreased ubiquitylation particularly in hematopoietic stem cells with subsequent activa-



▶ **Fig. 2** Bone marrow aspiration show vacuoles in myelomonocytic cells.

tion of the innate immune system leading to stimulation of several main cytokine pathways; interleukin (IL)-6, TNF-alpha and interferon [1].

Although the complete characterization of VEXAS syndrome is ongoing, almost all organ systems might be affected by the condition revealing a wide array of clinical manifestations including fever, bone marrow dysplasia, cytopenias, neutrophilic cutaneous and pulmonary inflammation, chondritis, unprovoked thrombosis, and vasculitis [7]. Our patient had developed several manifestations of disease including fever, severe fatigue, macrocytic anemia, thrombocytopenia, lymphopenia, leukocytosis, neutrophilic dermatitis, venous and arterial thrombosis, arthritis, myalgia, and myelodysplasia over two-year duration. Unfortunately, many of his symptoms emerged after he had COVID-19 causing a diagnostic challenge. To date the prognosis of COVID-19 among patients with VEXAS syndrome has not been reported but two COVID-19 related deaths were reported from the French cohort [2]

Also, symptoms of VEXAS syndrome may interfere with hematologic and vascular involvement of various autoimmune diseases like myelodysplastic syndrome [8]**. The VEXAS syndrome often overlaps with myelodysplastic syndromes (MDS) along with autoimmune diseases. Obiorah et al. previously reported that fifteen patients diagnosed as VEXAS syndrome has also met criteria of myelodysplastic syndrome** [9]**. Although VEXAS syndrome is described among autoinflammatory diseases, MDS may preceded to VEXAS syndrome, shared pathological pathways may be reported in the future. However, the relationship between VEXAS and MDS in patients with both disorders is even less clear**.

VEXAS syndrome is a treatment-resistant condition often having fatal outcome [1], including disease modifying anti-rheumatic drugs (DMARDs) and almost all biologic treatments (anti-TNF, anti-IL-1, anti-IL-6, anti-IL-17, CTLA4 agonist, anti-CD20) [10]. Corticosteroids are the mainstay of treatment with requiring higher doses to be effective. Other currently tried treatments are Janus kinase inhibitors and hematopoietic stem cell transplantation [2, 11]. **Azacitidine was also reported among treatment options in a study group who have MDS and VEXAS syndrome together and five of these 11 patients were successfully treated with azacitidine** [12].

In conclusion, VEXAS and long COVID are two new conditions with overlapping clinical presentations. Fever, chondritis, macrocytic anemia, and remarkably elevated acute phase response are clinical characteristics that might help to differentiate VEXAS syndrome from long COVID. Physicians must be aware of such a clinical condition because of its different treatment strategy and prognosis.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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