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UNMASKING MACROPHAGE ACTIVATION SYNDROME IN VEXAS SYNDROME: A DIAGNOSTIC CHALLENGE

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ABSTRACT

Introduction: Vacuoles, E1 Enzyme, X-linked, Auto-inflammatory, Somatic (VEXAS) syndrome is a late-onset autoinflammatory disease caused by somatic mutations in the UBA1gene. Macrophage activation syndrome (MAS) is a rare but life-threatening hyperinflammatory condition whose association with VEXAS syndrome remains poorly described.

Case description: We report three cases of MAS occurring in men aged 65 to 72 years with genetically confirmed VEXAS syndrome. In all cases, MAS was characterized by fever, recent-onset cytopenias, marked hyperferritinaemia, and a high probability of MAS according to the H-score (>93%). Bone marrow examination demonstrated haemophagocytosis in two patients and numerous activated macrophages in one. Extensive investigations failed to identify infectious, malignant, or drug-related triggers. In one patient, MAS preceded the diagnosis of VEXAS syndrome by several years. In the two others, MAS occurred during the course of established VEXAS disease and was considered a manifestation of disease flare. Treatment included high-dose corticosteroids, with additional anakinra in one patient and etoposide in another, resulting in rapid clinical and biological improvement. One patient experienced MAS relapse following granulocyte colony-stimulating factor exposure during azacitidine treatment, whereas no recurrence was observed in the other two patients during follow-up.

Conclusion: MAS appears to be an underrecognized and potentially severe complication of VEXAS syndrome that may occur in the absence of an identifiable infectious or malignant trigger. Diagnostic overlap between both conditions may delay recognition. MAS should be suspected in VEXAS patients presenting with acute cytopenias, marked hyperferritinaemia, and organ involvement. Early use of the H-score, bone marrow examination, and prompt immunosuppressive treatment are essential to improve outcomes.

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KEYWORDS

VEXAS syndrome, macrophage activation syndrome, hemophagocytic lymphohistiocytosis, UBA1 mutation, autoinflammatory disease

LEARNING POINTS

- Macrophage activation syndrome (MAS) may represent a severe flare manifestation of Vacuoles, E1 Enzyme, X-linked, Auto-inflammatory, Somatic (VEXAS) syndrome, even in the absence of an identifiable infectious, malignant, or drug-related trigger.
- The diagnosis of MAS can be challenging in VEXAS syndrome because both conditions share overlapping features, including systemic inflammation, cytopenias, hyperferritinaemia, and bone marrow abnormalities.
- Recent-onset cytopenias, marked hyperferritinaemia, and organ involvement in patients with VEXAS syndrome should prompt early assessment for MAS using the H-score and bone marrow examination, allowing rapid initiation of immunosuppressive therapy.

INTRODUCTION

Since its initial description in 2020[1], the clinical spectrum of Vacuoles, E1 enzyme, X-linked, autoinflammatory, Somatic (VEXAS) syndrome has expanded considerably[2,3]. It is a X-linked autoinflammatory disorder caused by somatic mutations in the UBA1 gene that primarily affects men over 50 years of age. VEXAS syndrome is characterized by systemic inflammation, haematological abnormalities, and a marked dependency on corticosteroids. Therapies targeting IL6 receptors, JAK inhibitors, and azacytidine, are being increasingly used to optimize disease control.

Macrophage activation syndrome (MAS) is a rare, life-threatening hyperinflammatory syndrome caused by uncontrolled activation of macrophages and cytotoxic T cells. Clinical and biological features include fever, hepatosplenomegaly, cytopenia, hyperferritinaemia, hypertriglyceridemia, and coagulopathy. While MAS is most frequently triggered by infections, autoimmune diseases, systemic autoinflammatory diseases or haematological malignancies, its association with VEXAS syndrome remains poorly described.

We report here three cases of MAS in patients with genetically confirmed VEXAS syndrome *(Table 1)*.

CASE DESCRIPTION

Case 1: A 72-year-old man, with a history of neutrophilic dermatosis treated with colchicine since 2016, was hospitalized in September 2018 for febrile confusion initially attributed to a urinary tract infection, which was subsequently ruled out. While confusion resolved quickly, fever and abdominal pain persisted, and imaging revealed splenomegaly and multiple mediastinal, intra- and retroperitoneal lymphadenopathy. Laboratory investigations showed C-reactive protein 377 mg/l, ferritin 5437 µg/l and new-onset cytopenias without hepatic cytolysis. The H-score indicated a 93% probability of MAS, and extensive infectious work-up was negative. Bone marrow biopsy revealed haemophagocytosis and features of myelodysplasia *(Fig. 1A and 1B)*. Anakinra (anti-IL1 therapy) was initiated, resulting in rapid clinical and biological improvement within four days. However, due to neutropenia under treatment, anakinra was discontinued after four days and not resumed. No recurrence of MAS occurred thereafter. The diagnosis of VEXAS syndrome was confirmed in 2021 with the identification of a hotspot somatic UBA1 mutation (p. M41T). Since then, clinical condition of patient has remained stable, with no relapse of MAS.

Case 2: A 69-year-old male patient with a history of prostate cancer had been diagnosed in 2018 with VEXAS syndrome (p.S56F UBA1 mutation). His case, previously reported[4], presented initially with biological inflammation, fever, neutrophilic dermatosis, and muscle involvement

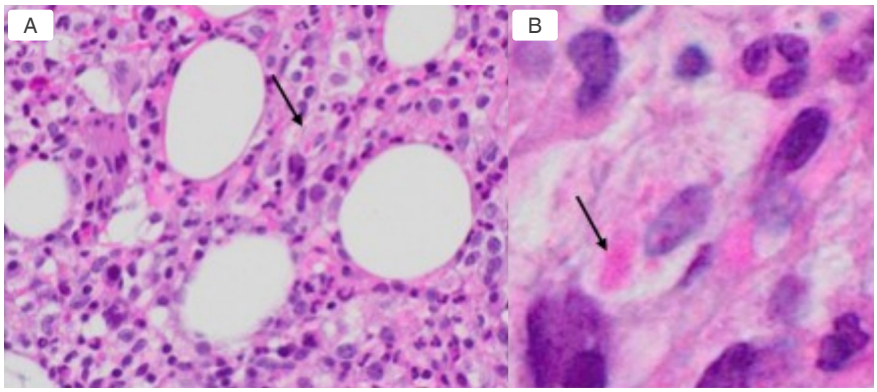


Figure 1. *Bone marrow biopsy. A) Bone marrow biopsy stained with haematoxylin-eosin-saffron (HES), × 400 magnification. The section shows haemophagocytosis (arrows), dysmegakaryopoiesis, dysgranulopoiesis, and loss of normal hematopoietic lineage distribution; B) Enlargement of panel A showing a macrophage with a phagocytosed red blood cell within the cytoplasm (arrow).*

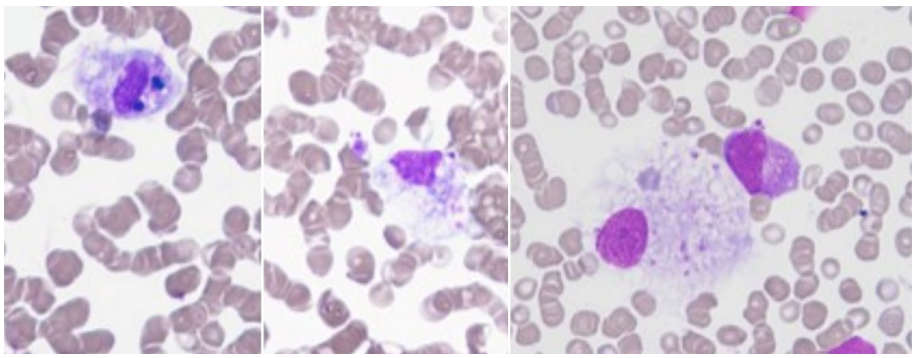


Figure 2. Bone marrow aspirate. Bone marrow aspirate stained with May-Grünwald-Giemsa (MGG), × 400 magnification, revealing numerous macrophages without evidence of typical features of haemophagocytosis or myelodysplasia.

(lower limb myalgia, trismus). Blood counts were normal at time of VEXAS syndrome diagnosis. He was responsive to corticosteroids but dependent to this therapy. Tocilizumab (anti-IL6 receptor) and later ruxolitinib (JAK inhibitor) failed to control symptoms. He was recently admitted to hospital to investigate weight loss, hepatalgia, recurrence of trismus and cytopenia while on prednisone 20 mg/day and ruxolitinib. Examination was unremarkable, but laboratory tests showed transaminase 20 N, ferritin 25,000 µg/l, recent normocytic anaemia (hemoglobin 90 g/l, MCV 95 fl) and thrombocytopenia (110 g/l), without white blood cells abnormality. The H-score indicated a 98% probability of MAS. Bone marrow aspirate revealed numerous macrophages without features of haemophagocytosis or myelodysplasia *(Fig. 2)*. Extensive etiological work-up including infectious, prostate cancer relapse and drug-induced MAS was negative. The diagnosis of MAS secondary to VEXAS flare was finally retained. Treatment with methylprednisolone pulses (250 mg/day during 3 days), then orally prednisone (1 mg/kg/day) and intravenous etoposide (100 mg/m^2, single dose) led to complete and rapid resolution of MAS and VEXAS features, including trismus regression, rapid improvement of the hepatic cytolysis, and normalization of the ferritin level within one week. Azacitidine was initiated subsequently, due to uncontrolled VEXAS syndrome. Following the second cycle, a febrile neutropenia required G-CSF support, which was followed by a relapse of macrophage activation syndrome at 3 months, requiring increased corticosteroids and etoposide therapy again.

Case 3: A 65-year-old man was diagnosed with VEXAS syndrome in 2020, initially presenting with a periarteritis nodosa-like phenotype including arthritis, rash, erythema nodosum, fever, and persistent inflammation. He was then treated for presumed systemic vasculitis before the genetic confirmation of UBA1 mutation. In April 2020, he was admitted for febrile dyspnoea and pancytopenia. Broad microbiological work-up, including blood, urine, and bone marrow cultures, was negative. Epstein-Barr virus was initially suspected based on a peripheral blood viremia, but not confirmed in bone marrow, making its role in the MAS episode difficult to establish. The H-score indicated >99% probability of MAS. This was supported by characteristic laboratory abnormalities and the presence haemophagocytosis on bone marrow aspirate *(Fig. 3A and 3B)*. Pulmonary involvement was attributed to a VEXAS flare. He received intravenous methylprednisolone (500 mg/day for 3 days), followed by oral corticosteroids (1 mg/kg/day). His hospital course was further complicated by mild disseminated intravascular coagulation requiring red blood cell and plasma transfusions. Ruxolitinib was initiated as maintenance therapy for VEXAS syndrome, without relapse of MAS at last follow-up.

DISCUSSION

The association between MAS and VEXAS syndrome remains underrecognized. Data from the French VEXAS group registry indicated that serious infections are common in VEXAS patients, which could act as a potential trigger for MAS[5]. In all three cases, no infectious or malignant trigger could be identified, supporting the assumption of a direct pathogenic link between MAS and the underlying VEXAS syndrome. This is in line with the few reports of MAS in VEXAS syndrome that were described in the absence of any identifiable infectious trigger[6].

Pathophysiologically, UBA1 mutations within the myeloid lineage disrupt ubiquitination and dysregulate innate immune signalling[1]. This results in an inflammasome activation and overproduction of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-18, and interferon-gamma (IFN-γ), driving macrophage hyperactivation and potentially MAS.

CONCLUSION

This case series illustrates the diagnostic complexity of

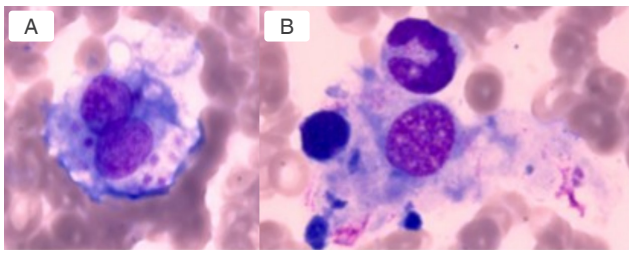


Figure 3. Bone marrow aspirate. A) Bone marrow aspirate stained with May-Grünwald-Giemsa (MGG), × 1000 magnification, showing a macrophage with evidence of typical features of haemophagocytosis (platelet phagocytosis); B) Bone marrow aspirate stained with May-Grünwald-Giemsa (MGG), × 1000 magnification, showing a macrophage that has phagocytosed a leukocyte and an erythroblast.

	Case 1	Case 2	Case 3
Sex / Age at MAS diagnosis	Male 72-year-old	Male 69-year-old	Male 65-year-old
VEXAS Syndrome			
UBA1 mutation	p.M41T	p.S56F	p.M41T
Clinical and laboratory features	Neutrophilic dermatosis Biological inflammation Fluctuating anaemia (nadir 9 g/dl in 2016). No other cytopenia	Fever Cutaneous rash Trismus with inflammation of the pterygoid muscles Biological inflammation No cytopenia	Fever Cutaneous rash Arthritis Headache Erythema nodosum Cutaneous vasculitis Biological inflammation No cytopenia
MDS	Yes	No	No
Treatments received for VEXAS syndrome before MAS	Colchicine	1st line: GCs 2nd line: Ruxolitinib + GCs 3rd line: Tocilizumab + GCs	1st line: GCs 2nd line: GCs + Methotrexate 3rd line: GCs + Cyclophosphamide 4th line: GCs + Rituximab 5th line: GCs + Cyclophosphamide
MAS			
Clinical features	- Fever - Confusion - Abdominal/lumbar pain - Multiple adenopathy - Splenomegaly	- Fever - Abdominal pain	- Fever - Dyspnoea
Laboratory features	- Ferritin 5437 µmol/l - Triglycerides 1.76 g/l - Fibrinogen 6.93 g/l Anaemia (8.6 g/dl). No other cytopenia	- Ferritin 22075 µmol/l - Triglycerides 3.07 g/l - Fibrinogen 1.46 g/l - Liver cytolysis 20 ULN - Bicytopenia (platelets 76 g/l, neutrophil 0,76 g/l)	- Ferritin 6094 µmol/l - Triglycerides 2,5 g/l - Fibrinogen 0,7 g/l - Pancytopenia (haemoglobin 8 g/dl, platelet 109 g/l, Neutrophil 0,2 g/l)
Bone marrow features	Bone marrow biopsy: MAS and MDS	Bone marrow aspiration: Presence macrophages, with no evidence of MAS	Bone marrow aspiration: MAS without MDS
H-score	93 %	98 %	>99 %
Treatment	Anakinra 100 mg/d SC	Methylprednisolone bolus d1 to d3 250 mg/bolus then relay prednisolone 1 mg/kg/d with rapid tapper to 20-30 mg/d Etoposide 100 mg/m^2 (single perfusion)	3 bolus of Methylprednisolone (500 mg/bolus) then relay Prednisolone 1 mg/kg with decrease Transfusion support for disseminated intravascular coagulation: red blood cells and plasma
Outcomes	Discontinuation of Kineret at day 4 due to neutropenia and urticarial rash	4th line treatment: GCs + Azacytidine	6th line treatment: GCs + Ruxolitinib
Follow up	No relapse of MAS at 7 years	Relapse of MAS at M3 after 2 cycles of Vidaza, likely-triggered by G-CSF support	- No relapse of MAS at 5 years - Relapse of VEXAS at 4 years: Vidaza introduction leading to remission at M6

Table 1. *MAS in patients with genetically confirmed VEXAS syndrome.*

Abbreviations: MDS, myeloplastic syndrome; MAS, macrophage activation syndrome; VEXAS, vacuoles, E1 enzyme, x-linked, auto-inflammatory, somatic; UTI, urinary tract infection; SC, subcutaneous; ULN, upper limit of normal; GCs, glucocorticoids.

MAS in VEXAS syndrome. Indeed, clinical, biological and histological overlap may obscure and delay the diagnosis of MAS. We suggest that MAS should be considered as a potential complication of VEXAS flare presenting with recent cytopenia, hyperferritinaemia and/or organ involvement, even in the absence of any infection. The early use of predictive tools such as the H-score and the use of bone marrow aspiration shout not be delayed. Prompt immunosuppressive treatment, including high-dose corticosteroids and targeted therapy, appears effective in treating MAS in VEXAS syndrome.

Further studies are needed to better define the incidence, pathophysiology, and optimal therapies for MAS-associated VEXAS syndrome.

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