CASE REPORT

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Different Clinical Presentations of Monogenic Vexas Syndrome

Mine KARADENİZ[a], Ümit Yavuz MALKAN[b], Yahya BÜYÜKAŞIK[b]

[a]University of Health Sciences Gülhane Training and Research Hospital, Division of Hematology, Ankara, Türkiye
[b]Hacettepe University Faculty of Medicine, Division of Hematology, Ankara, Türkiye

ABSTRACT Vexas syndrome is caused by an X-linked somatic mutation in which haematological manifestations and autoimmunity are intertwined. The clinical course can be very diverse and marrow manifestations seen especially in myelodysplastic syndrome are observed. There is no specific agent in the treatment and the treatments used in myelodysplastic syndrome come to the fore. In this article, we wanted to describe the different clinical courses of our cases with Vexas syndrome. Although the syndrome resembles myelodysplastic syndrome in terms of haematological findings, it is in a quite different spectrum in terms of clinical course. It may present with simple anaemia or complicated thromboembolic events and mortality.

Keywords: Haematology; mortality; myelodysplastic syndromes; UBA1 protein

Vexas syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a monogenic disease characterised by clinical variety with a predominance of inflammatory process and hematologic findings resulting from somatic mutation in the X-linked UBA1 gene involved in protein ubiquitination.[1] The syndrome may present with mild symptoms as well as an aggressive progressive clinical course involving life-threatening thrombotic events. Although cytoplasmic vacuolization in the myeloid precursor series is an important and valuable finding in bone marrow sampling, it is not diagnostic nor specific to this syndrome. The use of a specific agent in treatment has not yet been established.

All patients were diagnosed with Vexas syndrome after peripheral blood samples were analysed for UBA-1 gene mutation by next-generation sequencing in a refereed laboratory in the U.S.A. Informed consent was obtained from all of the three patients or from their relatives during the preparation of this publication.

CASE REPORTS

CASE 1

A 64-year-old male patient admitted to an external centre with a diagnosis of immunoglobulin G4-related disease with complaints of acute phase elevation, macrocytic anaemia, fever and swelling in the right eye. Other organ and system examinations revealed no additional disease. He did not recover despite the use of immunosuppressive agents for one year. The UBA1b (p. Met 41 Leu) gene defect was identified in the patient who had vacuolization in the myeloid series and dysplastic findings in two series in bone marrow examination due to dysplasia and macrocytic anaemia in peripheral smear. The patient's IPSS and IPSS-R score was 0 and 2 respec-

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Correspondence: Mine KARADENİZ
University of Health Sciences Gülhane Training and Research Hospital, Division of Hematology, Ankara, Türkiye
E-mail: drminekrdnz@gmail.com

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tively. Hypomethylating agent (HMA) 5-azacytidine treatment (7 days, subcutan at a dose of 75 mg/m^2/day for 28-day cycles) started with the diagnosis of Vexas syndrome and concurrent low risk myelodysplastic syndrome (MDS). In the end of the second month of the HMA treatment, the evaluation of the patient showed improvement in cytopenias, regression in symptoms and acute phase response.

CASE 2

A 50-year-old male patient diagnosed with MDS without excess blast on hematologic examination due to episodic fever and accompanying neutropenia despite steroid use for relapsing polychondritis. After 12 cycles of 5-azacytidine treatment, fever episodes regressed, steroid dependency disappeared and the patient was followed up periodically with complete hematologic remission. Three years later, he presented with cytopenias and concurrent polychondritis attacks. The laboratory results of the patient was as following mean corpuscular volume (MCV): 116.2 fL (80-100 fL), the sedimentation rate (SR): 79 mm/hour (0-20 mm/hour), C-reactive protein (CRP): 29 mg/dL (0-0.8 mg/dL), fibrinogen: 686 mg/dL (180-350 mg/dL) and ferritine: 1124 mcg/L (20-336 mcg/L) and the thoracic computed tomography was normal. The bone marrow evaluation revealed 7-8% blasts and MDS-related findings. Since the patient had already received 5-azacytidine before, decytabine treatment was initiated by the diagnosis of high-risk MDS with an IPSS-R score of 5. After two cycles of decytabine (5 days, intravenous 20 mg/m^2/day for 28-day cycles) chemotherapy, the symptoms of polychondritis regressed but haematological improvement did not occur. The control of bone marrow examination revealed vacuolization of myeloid and erythroid precursors as well as leukemic transformation. After induction and consolidation treatments, haploidentical stem cell transplantation from his son was performed. In the light of clinical findings, UBA1 (p. Met 41 Thr) gene mutation which was ordered before transplantation, was found to be present in this patient.

CASE 3

A 64-year-old male patient presented with malaise, fever and hard, painful nodular lesions all over the body, especially on the extremities. The elevated MCV (100.6 fL), SR (120 mm/hour), CRP (30.8 mg/dL), fibrinogen level (825 mg/dL) and hyperferritinemia (1,105 mcg/L) was observed in the blood tests. Pulse steroid treatment was started with a prediagnosis of vasculitis. The thoracic computed tomography showed ground glass densities. Bone marrow aspiration performed in the diagnostic evaluation and revealed dysplastic findings and vacuoles in the myeloid precursor series. The UBA1 (p. Met 41 Val) gene mutation positivity identified. 5-azacytidine treatment with the standard protocol started because of a rapidly progressive clinical course. Three days after the end of the first course of 5-azacytidine, the patient underwent right upper thigh amputation due to ischemic findings in the right lower extremity, near total occlusion of the right femoral artery and gangrenous tissue formation. The patient died due to postoperative septic shock, recurrent thrombosis attacks and resistant infections.

DISCUSSION

Vexas syndrome, with its genetic background and clinical diversity has recently been defined and is just beginning to be understood. It is a difficult disease in terms of diagnosis, clinical behaviour and treatment with limited data. Protein ubiquitination defects due to mutation in the UBA1 gene on the X chromosome, unfolded protein response, misfolded protein accumulation and activation of immune pathways are defined as potentially responsible mechanisms in explaining the physiopathology of the syndrome.[2,3]

Vexas syndrome may present with macrocytic anaemia as in our first case.[4] In a series of 16 cases of Vexas, macrocytic anaemia was detected in all.[5] Hematologic malignant and premalignant diseases that can be identified in this syndrome include myeloid neoplasms such as MDS, MDS/myeloproliferative disease, acute myeloid leukaemia, B cell neoplasms, multiple myeloma and monoclonal gammopathy of uncertain significance. The association of Vexas syndrome with MDS is the most commonly reported hematologic disorder.[5,6] Demographic, clinical characteristics and outcomes of our patients are summarised in Table 1. Autoimmune diseases and inflammatory conditions like relapsing polychondritis,

TABLE 1: Demographic characteristics and results/outcomes of the three cases.

	Case 1	Case 2	Case 3
Age (y)	64	50	64
Gender	M	M	M
Haematological findings	Macrocytic anemia	Neutropenia, dysplasia findings in pheripheral smear sample	Macrocytosis and hyperfibrinogenemia
Co-morbidity	No	Relapsing policondritis	No
Bone marrow findings	Vacuolization in the myeloid series and dysplastic findings in two series	7-8% blasts and MDS- related findings, myeloid vacuolization	Dysplastic findings and vacuoles in the myeloid precursor series
Genetic Mutation	p. Met 41 Leu	p. Met 41 Thr	p. Met 41 Val
Treatment	HMAs	Haploidentical HSCT later HMAs failure	Pulse steroid, HMAs and intensive care unit support
Complications	No	Transplant-associated skin GVHD	Systemic vasculitis/recurrent arterial and venous embolism
Outcomes	Continuation of treatment with complete response	Following-up with full chimerism	Mortality

GVHD: Greft versus host disease; HMAs: Hypomethylating agents; M: Male; MDS: Myelodysplastic syndrome.

rheumatoid arthritis can be seen in MDS and chronic myelomonocytic leukaemia at rates ranging from 15% to 35%.[7,8] In the study in which 514 cases diagnosed with MDS were evaluated, rheumatoid arthritis was the most common autoinflammatory process accompanying MDS and Vexas syndrome was detected in only one case.[9] In another multicenter study, pathology compatible with MDS was found in 50% of 116 patients followed up with Vexas syndrome, and also the prognosis was poorer in this group.[10] It is suggested that Vexas syndrome should be evaluated as a separate hemato-inflammatory disease from MDS. The cytogenetic presentation is less heterogeneous and co-mutation accompaniment is rarely reported in this syndrome.[11] In the retrospective analysis of cases in which vacuolization was reported in myeloid precursors in the bone marrow evaluation, 38.6% of MDS and 2.9% of Vexas syndrome detected.[12] Figure 1 shows the vacuolization in bone marrow sample in Vexas syndrome.

Thrombotic process, which resulted in mortality in our last case, plays an important role in the prognosis of the syndrome. Chronic inflammation, endothelial damage, increased leukocyte activity, detection of elevated lupus anticoagulant positivity (44-69%) and abnormal factor 8 level may play a role in the predisposition to thrombotic events.[3] The incidence of venous thrombosis between 12% and 63% and arterial thrombosis at rates ranging from 1.6-33% has been reported in different studies.[10]

Treatment of Vexas syndrome is based on the use of HMAs Janus kinase inhibitors (JAKi) such as ruxolitinib. The efficacy of azacytidine in Vexas syndrome was approximately

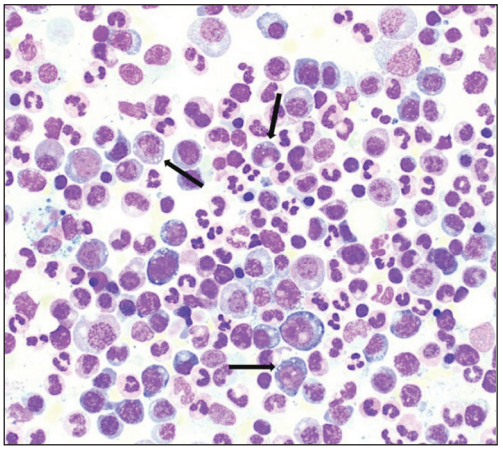

FIGURE 1: May Grünwald-Giemsa (MGG) stained marrow aspiration specimen. Microscopic image magnification ratio (x100).
Black arrows show the vacuolization in myeloid precursor cells.

46%.[13] There are two cases showing a 60% and 82% response with JAKi ruxolitinib at 6 months and a case report of a patient treated with another JAKi, filgotinib.[14] In a case report of a stem cell recipient patient from a mismatched donor, demonstration of clearance at allelic frequency of UBA1 gene mutation can be considered as a sign that transplantation may be beneficial in selected cases.[15]

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mine Karadeniz, Yahya Büyükaşık;* ***Design:*** *Mine Karadeniz;* ***Control/Supervision:*** *Ümit Yavuz Malkan, Yahya Büyükaşık;* ***Data Collection and/or Processing:*** *Mine Karadeniz;* ***Analysis and/or Interpretation:*** *Mine Karadeniz;* ***Literature Review:*** *Mine Karadeniz;* ***Writing the Article:*** *Mine Karadeniz, Ümit Yavuz Malkan;* ***Critical Review:*** *Ümit Yavuz Malkan, Yahya Büyükaşık.*

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