

Wernicke's Encephalopathy in a Child with Acute Lymphoblastic Leukemia

Akut Lenfoblastik Lösemili Bir Çocuk Hastada Wernicke Ensefalopatisi

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To the Editor,

We read with great interest the article "A rare complication developing after hematopoietic stem cell transplantation: Wernicke's encephalopathy" by Solmaz et al. [1]. Wernicke's encephalopathy (WE) is an acute syndrome requiring emergent treatment to prevent death and neurologic morbidity [2]. While most often associated with alcoholism, WE also occurs in the setting of prolonged intravenous feeding without adequate thiamine supplementation, prolonged starvation or unbalanced nutrition, gastrointestinal surgery, systemic malignancy, and transplantation [3]. The classic triad of WE includes encephalopathy, oculomotor dysfunction, and gait ataxia. In their article, Solmaz et al. reported a patient who developed WE following hematopoietic stem cell transplantation (HSCT) and they concluded that this was due to prolonged total parental supplementation and lack of thiamine supplementation. The only other suggested cause was the use of busulfan in the conditioning regimen. In the literature there is a link of WE to HSCT, malignancies, or chemotherapies. Here we report a new patient who developed WE during acute lymphoblastic leukemia (ALL) treatment.

A 13-year-old female patient diagnosed with intermediate risk group ALL developed severe neutropenia after a high-dose methotrexate block and oral Purinethol (BFM protocol M). Ceftazidime and fluconazole treatment was started due to fever. After 3 days the patient had poor oral intake and received total parenteral nutrition (TPN) containing protein and dextrose. On the 6th day of TPN she had fever, abdominal pain, nausea, and bilious vomiting. Her abdominal ultrasound revealed typhlitis. Ceftazidime-fluconazole treatment was switched to meropenem and L-amphotericin and oral intake was stopped. On the 8th day of TPN, the patient developed confusion, altered mental status, horizontal nystagmus, and lateral gaze paralysis in the right eye. Her brain computed tomography (CT) was normal. However, brain magnetic resonance imaging (MRI) showed increased signal in the bilateral thalamic pulvinar and

mammillary bodies in the axial fluid-attenuated inversion recovery (FLAIR) sequence (Figure 1). These were concluded to be classic findings of WE [4]. Intramuscular thiamine at 200 mg three times a day for the first 3 days (600 mg/day total), 100 mg two times a day for the next 3 days (200 mg/day total), and 100 mg thiamine daily for the last 3 days was given. A rapid improvement of neurologic symptoms was observed on the third day of thiamine treatment. The patient's thiamine level was 55 mg/L and 125 mg/L before and after the treatment, respectively (normal range: 25-75 mg/L). She was discharged from the hospital with good oral intake and normal neurological examination.

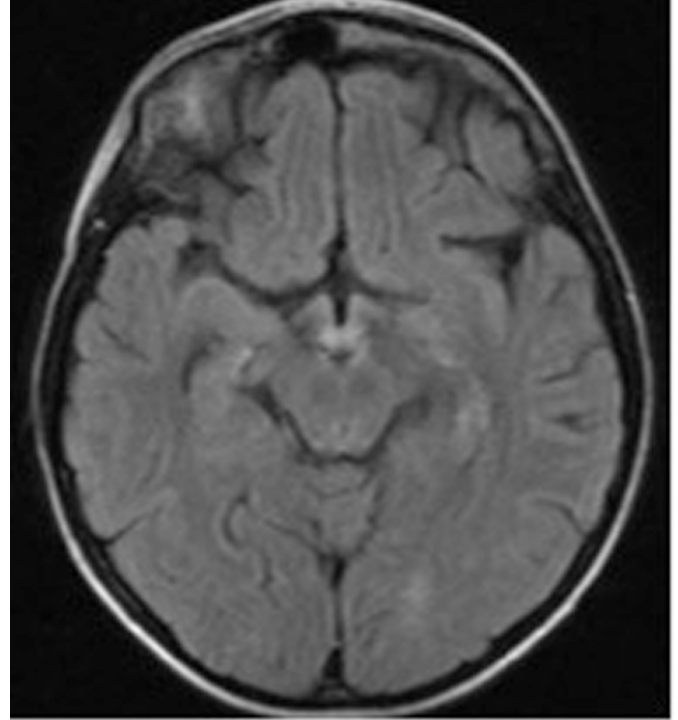


Figure 1. Increased signal in the bilateral thalamic pulvinar and mammillary bodies in the axial fluid-attenuated inversion recovery sequence.

WE is primarily a clinical diagnosis. Response to treatment may be diagnostic. The sensitivity and specificity of serum thiamine level in symptomatic patients is unclear, as the blood level may not reflect the brain thiamine level. A normal blood thiamine level, as in our patient, does not exclude the possibility of WE with MRI findings [5]. MRI is more sensitive than CT in WE [6]. In conclusion, all at-risk patients with undiagnosed altered mental status, oculomotor disorders, or ataxia must be evaluated for WE. Further studies are needed for examining the possible role of chemotherapeutics in the development of WE.

Keywords: Wernicke's encephalopathy, Thiamine deficiency, Pediatric leukemia

Anahtar Sözcükler: Wernicke ensefalopatisi, Tiamin eksikliği, Pediatrik lösemi

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Comment: In Response to “Megaloblastic Anemia with Ring Sideroblasts is not Always Myelodysplastic Syndrome”

Yorum: “Halka Sideroblastlı Megaloblastik Anemi Her Zaman Miyelodisplastik Sendrom Olmayabilir”e Yanıt

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To the Editor,

I read the letter “Megaloblastic Anemia with Ring Sideroblasts is not Always Myelodysplastic Syndrome” by Narang et al., recently published in this journal [1]. The manuscript is well written with a description of a very informative case of megaloblastic anemia with ring sideroblasts in a young female of 18 years old. Ring sideroblasts are associated with abnormal expression of several genes of heme synthesis or mitochondrial iron processing [2]. After exclusion of non-neoplastic causes of ring sideroblasts such as congenital/hereditary sideroblastic anemia and acquired reversible sideroblastic anemia (drugs, toxins, or nutritional deficiency), myelodysplastic syndrome (MDS) can be strongly suspected, particularly in elderly patients. The presence of ring sideroblasts alone is not sufficient for a diagnosis

MDS; the presence of refractory cytopenia(s) is a prerequisite. Refractoriness can only be established after exclusion of secondary causes, most importantly nutritional deficiencies. After that, a complete evaluation of the erythroid, myeloid, and megakaryocytic lineages of bone marrow is essential. At least 15% ring sideroblasts are required for the diagnosis of MDS with ring sideroblasts (MDS-RS) in cases lacking mutations in the spliceosome gene *SF3B1*. *SF3B1* mutations are found in 60%-80% of patients with refractory anemia with ring sideroblasts (RARS) or RARS with thrombocytosis (RARS-T) and are associated with favorable prognosis [3]. In the recent World Health Organization (WHO) 2016 classification, cases with ring sideroblasts and multilineage dysplasia without excess blasts or isolated del (5q) abnormality are categorized as MDS-RS. Recent

studies have shown that the percentage of ring sideroblasts in MDS is not prognostically important. Thus, in the revised WHO classification, a diagnosis of MDS-RS may be made even in the presence of only 5% of ring sideroblasts in cases with *SF3B1* mutation. MDS-RS cases will be subdivided into cases with single lineage dysplasia (previously classified as RARS) and cases with multilineage dysplasia (previously classified as refractory cytopenia with multilineage dysplasia). Furthermore, RARS-T has been accepted as an entity and termed MDS/myeloproliferative neoplasm (MPN) with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) in the 2016 classification. Unlike MDS-RS, the number of ring sideroblasts required for a diagnosis of MDS/MPN-RS-T is 15%, irrespective of the presence or absence of a *SF3B1* mutation [4]. As described in the case of Narang et al., in a young female of 18 years old without a history of persistent refractory cytopenia(s), a diagnosis of MDS can only be established after exclusion of secondary causes such as nutritional deficiencies [1]. An adequate trial with hematinics (vitamin B12, folic acid, and pyridoxine) is needed in such cases. After exclusion of secondary causes, if cytopenia(s) still persists, a repeat bone marrow examination with cytogenetic and molecular studies can be considered to establish the diagnosis of a clonal hematopoietic disease such as MDS or MDS/MPN.

Keywords: Refractory anemia with ring sideroblasts, RARS with thrombocytosis, Myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis

Anahtar Sözcükler: Halka sideroblastlı refrakter anemi, Trombositoz ile birlikte RARS, Halka sideroblast ve trombositoz ile birlikte miyelodisplastik sendrom/miyeloproliferatif neoplazi

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Therapeutic International Normalized Ratio Monitoring

Terapötik Uluslararası Normalleştirilmiş Oran İzlemi

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To the Editor,

The report on "Warfarin dosing and time required to reach therapeutic international normalized ratio in patients with hypercoagulable conditions" was very interesting [1]. Kahlon et al. concluded that "Patients with hypercoagulable conditions require approximately 10 mg of additional total warfarin dose and also require, on average, 2 extra days to reach therapeutic international normalized ratio (INR) as compared to controls."

The big concern in this report regards the technique used for INR measurement. Kahlon et al. did not mention this and might not have noted the problem of measurement of INR in the follow-up of the patient. The quality control of the measurement is very important and measurements from different laboratory techniques and settings can be a factor leading to error in laboratory results [2,3]. It is noted that the local calibration in correcting the variability in INR determination and the difference between batches has to be controlled [4].

Keywords: Monitoring, International normalized ratio, Hemostasis

Anahtar Sözcükler: İzlem, Uluslararası normleştirilmiş oran, Hemostaz

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Iron Overload in Hematopoietic Stem Cell Transplantation

Hematopoetik Kök Hücre Transplantasyonunda Aşırı Demir Yüklenmesi

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To the Editor,

We read the publication entitled "Current Review of Iron Overload and Related Complications in Hematopoietic Stem Cell Transplantation" with great interest [1]. As summarized by Atilla et al. [1], "Organ dysfunction due to iron overload may cause high mortality rates and therefore a sufficient iron chelation therapy is recommended". We would like to share the experience from our settings where there is a very high prevalence of thalassemia and transplantation is the only curative treatment.

Iron overload is common among transfusion-dependent thalassemia patients and transfusion during transplantation might increase the risk of the complication of iron overload. However, in clinical practice, the problem is not common and improvement of the patients after transplantation is reported. According to the recent report by Inati et al. [2], with standard chelation therapy, the outcome of thalassemic patients undergoing stem cell transplantation is usually favorable. The use of the standard dosage of deferoxamine, with or without phlebotomy, accompanied with close iron status monitoring can be effective [2,3]. It can be seen that stem cell transplantation can be problematic despite there being a need of hypertransfusion

during the process even though the patient might have an underlying severe iron overload condition such as thalassemia.

Keywords: Iron, Overload, Hematopoietic stem cell, Transplantation

Anahtar Sözcükler: Demir, Aşırı yüklenme, Hematopoietik kök hücre, Transplantasyon

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Reply

Dear Sora Yasri,

Thank you very much for your valuable comments and sharing your experience. We agree for your contribution. In thalassemia patients, several transplantation centers categorised risk factors prior to allogeneic hematopoietic stem cell transplantation. Pesaro classification assigned patients to three arms according to the absence or presence of one, two or three risk factors: hepatomegaly > 2 cm, portal fibrosis, and irregular chelation history [1]. It should be kept in mind that in a study by Ghavamzadeh et al., liver iron overload did not change after transplant ($p=0.61$) but hepatic fibrosis progressed ($p=0.01$) [2]. Allogeneic stem cell transplantation did not reduce liver iron overload and in fact liver fibrosis increased. Also steps for reducing iron overload should be taken in the post transplant setting [3]. Iron overload is still an essential issue in both pre

and post transplant settings. Survival in transfusion-dependent thalassemia patients can be improved with proper understanding of the pathophysiology of thalassemia and iron toxicity.

Regards,

Erden Atilla, Selami K. Toprak, Taner Demirer

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Sole Infrequent Karyotypic Aberration Trisomy 6 in a Patient with Acute Myeloid Leukemia and Breast Cancer in Remission

Akut Miyeloid Lösemi ve Remisyonunda Meme Kanseri Hastada Nadir İzole Karyotipik Bozukluk

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To the Editor,

Cytogenetic abnormalities play important roles in the diagnosis and prognosis of leukemias [1]. Trisomy 6 as the sole karyotypic aberration is infrequent in leukemias [1,2]. A 50-year-old female patient presented with fatigue. She had been treated by mastectomy and given chemotherapy (no further information available) for breast cancer 3 years ago. She had been using tamoxifen for 3 years. Her breast cancer was in remission. Physical examination was consistent with a pale appearance. Hemoglobin, neutrophils, and platelet count were 8.5 g/dL, 900/ μ L, and 11,000/ μ L, respectively, on admission. In the peripheral blood smear, there were dysplastic features in monocytes and a few blasts were reported. In flow cytometry, CD13, CD33, CD34, CD45, CD117 (c-kit), HLA-DR, and MPO were positive. Bone marrow aspiration and biopsy revealed hypercellularity with

dysplastic and megaloblastic features in erythroid series, grade 1/3 reticulin fibrosis, and 24% blasts without ring sideroblasts, which in turn with cytometry findings were accepted as evidence of acute myeloid leukemia (AML). Bone marrow cytogenetic analysis revealed trisomy 6 (47,XX, +6 [20]) in all the metaphases (Figure 1). The patient was not in remission after the first induction treatment and she passed away due to septic shock during the second induction treatment.

Chromosome aberrations detected in therapy-related AML (t-AML) and de novo AML cases are identical but their frequencies may differ [3]. In a series at the University of Chicago, normal karyotypes were seen in 9.6% of t-AML cases [4]. In the report of Godley and Larson, among 306 patients with t-AML, 32 had solid breast cancer as the primary diagnosis [5]. Alkylating exposures and topoisomerase II inhibitors are associated with

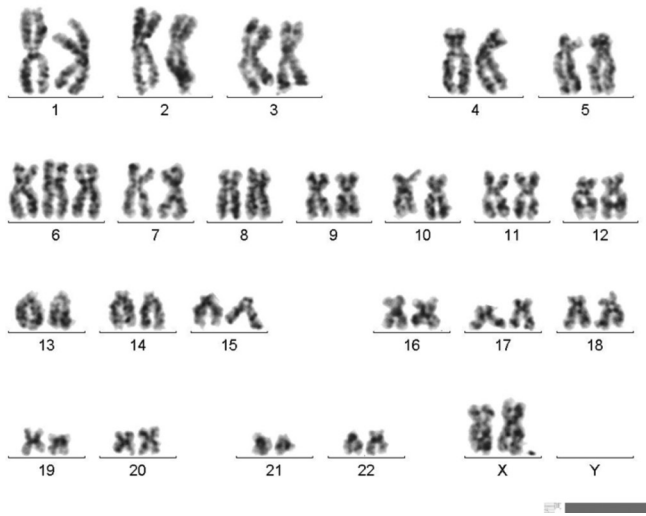


Figure 1. Bone marrow cytogenetic analysis revealed trisomy 6 (47,XX, +6 [20]) in all the metaphases.

t-AML [3,6]. Godley and Larson mentioned granulocyte colony-stimulating factor usage as a risk factor in t-AML after breast cancer [5]. Unfortunately, we do not know which agents were given for our patient's breast cancer.

Autosomal trisomies have been described in several hematologic malignancy cases. The first case of sole trisomy 6 was reported in aplastic anemia. Other reports showed that trisomy 6 was associated with hypoplastic bone marrow, dyserythropoiesis, and AML [7]. Mohamed et al. reviewed 7 patients with trisomy 6. Patients presenting with overt AML had hyperplastic marrows [8]. Our patient had hypercellular marrow, as well. Mohamed et al. also reviewed the literature and found 4 MDS cases among 22 patients with trisomy 6 [8]. The marrow examination of this case revealed secondary dysplastic leukemia. The patient of Gupta et al. had de novo AML and did not respond to the first remission induction treatment [1].

Yu et al. reviewed ten reports in PubMed describing 18 cases of AML presenting with trisomy 6 as the sole karyotypic abnormality along with 3 cases of their own [7]. They concluded

that there were no direct correlations between the number of blasts and the percentage of abnormal metaphases. They could not identify any correlation between morphology or prognosis and trisomy 6 [7].

Under these circumstances, as in our case, we lack information on the impact of trisomy 6 on prognosis in secondary AML patients.

Keywords: Trisomy 6, acute myeloid leukemia, Breast cancer

Anahtar Sözcükler: Trizomi 6, Akut miyeloid lösemi, Meme kanseri

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Premarital Genetic Diagnosis Revealed Co-heredity Nature of Beta Globin Gene 25-26 del AA and 3'UTR+101 G-C Variants in Two Beta Thalassemia Heterozygotes

İki Heterozigot Beta Talasemi Taşıyıcısında Evlilik Öncesi Genetik Tanı ile Beta Globin Geni 25-26 del AA ve 3'UTR+101GC Varyant Kalıtımının Gösterilmesi

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To the Editor,

Over 2000 gene variants were reported in the beta globin gene, including hemoglobin variants. These variants are important from clinical and genetic counseling points of view [1,2]. Recently a genetically related Turkish couple was referred to our department for genetic counseling for beta thalassemia carrier status. During premarital screening they were both diagnosed as beta thalassemia carriers by high pressure liquid chromatography analysis and whole blood count (Table 1). Genomic DNAs of both patients were extracted using the QIAamp DNA Blood Midi Kit (QIAGEN, Germany). The *HBB* gene was amplified using the following polymerase chain reaction (PCR) primers: forward (5'GCCAAGGACAGGTACGGCTG3'), reverse (5'CCCTTCCTATGACATGAACCTAACCAT3') and forward (5'CAATGTATCATGCCTCTTGCACC3'), reverse (5'GAGTCAAGGCTGAGGATGCGGA3'). Purifications were done using the ExoSAP purification program (Affymetrix Inc., USA). The BigDye Sequencing PCR technique was used for the analysis (Applied Biosystems, USA). Samples were analyzed with the SeqScape v2.5 analysis program. Common alpha globin gene deletions were analyzed according to the previously reported technique [3,4].

Two different gene alterations were found in the beta globin gene of both partners (Table 1). One of them was a deletion at 25-26AA (rs35497102) (Figure 1). The other gene alteration was a single nucleotide polymorphism at 3'UTR+101 G-C +233 relative to the termination codon (rs12788013) (Figure 2). Neither of the individuals carried the common alpha thalassemia deletions.

Beta globin gene 3'UTR+101 G-C alteration is a single nucleotide polymorphism that was not previously classified and reported as a pathogenic variant [1,2]. It seems that carrying 3'UTR+101 G-C does not cause any additional clinical features in 25-26 del AA carriers. In this situation there is certainly more than one possibility to be mentioned in genetic counseling. 3'UTR+101 G-C being a single nucleotide variant resulting in a decreased expression of the gene causing the beta thalassemia major clinical picture is the most likely one. This is more evident when combined with a disease causing mutation, as previously reported by us and others [3,4,5,6,7]. However, from our family's data, this is not valid, because they are beta thalassemia carriers. The main problem in this case is that an expression study was not performed for these individuals.

Table 1. Whole blood count, hemoglobin A2 levels, and *HBB* gene mutation profile of the couple.

	Hb	RBC	MCV	MCH	MCHC	RDW	HbA2	HbF	<i>HBB</i> gene variant
Male	10.7	5.78	55.5	18.5	33.3	18.5	4.8	1.4	Variant 1: c.25_26AA (rs35497102) Variant 2: 3'UTR+101 G-C +233 relative to termination codon (rs12788013)
Female	11.3	5.93	56.8	19.1	33.5	18.2	4.4	2.9	Variant 1: c.25_26AA (rs35497102) Variant 2: 3'UTR+101 G-C +233 relative to termination codon (rs12788013)

Hb: Hemoglobin, RBC: red blood cell, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width.



Figure 1. Sequencing data of the deletion at 25-26 AA (rs35497102).

One of the possibilities for the inheritance pattern in this situation is that these two gene variants will be inherited in the "cis" position. In this case, from the genetic point of view, "in cis" is the only acceptable solution for the fetus, which will be similar to the parents. However, if it does not come in the "cis" position, there will be a possibility that the fetus may inherit 3'UTR+101 G-C in the homozygous state (from both parents). Unfortunately, not many publications have discussed similar conditions. For prenatal screening of the fetus, only the del 25-26 AA /3'UTR+101 G-C heterozygote state should be accepted as normal.

This case report highlights the need for investigating partnered beta thalassemia carriers by complete sequencing analysis of the beta globin gene if only one pathogenic mutation is detected by first-tier methods for the possibility of providing appropriate genetic counseling for couples at risk during prenatal genetic diagnosis.

Keywords: Thalassemia, Variant, Genetic counseling, Prenatal diagnosis, Beta globin gene, Turkish

Anahtar Sözcükler: Talasemi, Varyant, Genetik danışmanlık, Prenatal tanı, Beta globin geni, Türk

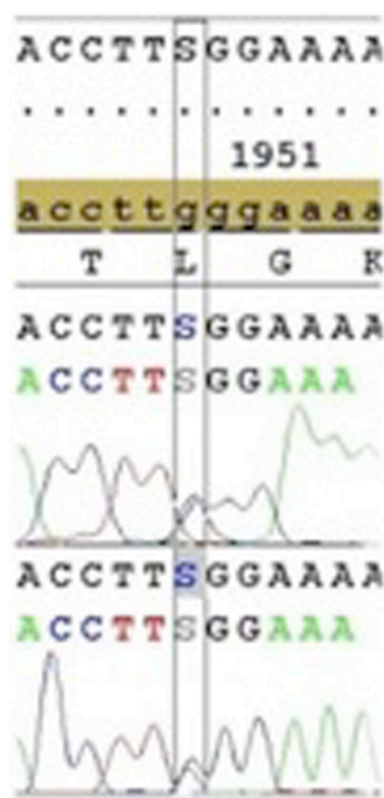


Figure 2. Single nucleotide polymorphism at 3' UTR +101 G-C (+233 relative to termination codon).

Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Acute Myocardial Infarction Due to Eltrombopag Therapy in a Patient with Immune Thrombocytopenic Purpura

İmmün Trombositopenik Purpurası Olan Bir Hastada Eltrombopag Tedavisine Bağlı Akut Miyokard İnfarktüsü

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To the Editor,

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by anti-platelet antibody-mediated platelet destruction and anti-megakaryocyte antibody-mediated impairment of platelet production, which may cause bleeding [1]. Coexistence of ITP and coronary artery disease (CAD) is rare. Patients with ITP have increased risk of thrombosis and atherosclerosis associated with larger platelets more adhesive to vascular surfaces, direct endothelial damage [2], and negative effects of therapy with steroids [3] or intravenous immunoglobulin [4]. We present here a 61-year-old male patient who was diagnosed with ITP and presented with acute myocardial infarction while undergoing eltrombopag therapy.

A 61-year-old man was admitted to our emergency room with typical chest pain lasting for last 3 days. He had been diagnosed with ITP 5 years ago. His medical history was remarkable for splenectomy 6 months after the diagnosis of ITP. He was in remission for 4 years after the splenectomy and he was not on any medication for 5 years. Four months before, during a routine check-up, relapse of disease had been noticed. Steroid therapy was initiated after relapse and administered with a tapering dosage for 3 months. The clinician did not observe adequate increase in the amount of platelets; therefore, eltrombopag (1x50 mg tablet) was initiated as a newline therapy 1 month ago. In the first 3 weeks, the platelet count did not increase adequately (platelets were about 13,000/mL), but in the last week before his admission to the emergency room his platelet count escalated to about 105,000/mL. The patient was admitted to our emergency room with typical chest pain. His baseline cardiovascular risk factors, among smoking, hyperlipidemia, hypertension, diabetes mellitus, and family history, were not remarkable. The patient was not on any medication apart from eltrombopag therapy. On his admission, electrocardiography showed ST segment elevation in leads DII-III-AVF and V5-6 with pathological Q waves, which gave rise to consideration of sub-acute inferolateral myocardial infarction. Primary percutaneous coronary intervention (PCI) was performed immediately. Coronary angiography demonstrated the anomalous origin of the coronary artery. The circumflex coronary artery (CX) originated from the right aortic root. There was plaque on the proximal and middle portion of the left anterior descending

artery and proximal portion of the CX, and subtotal occlusion at the distal portion of the right coronary artery (RCA). A bare metal stent was implanted at the lesion site and post-dilatation was performed (Figures 1A-1D). After PCI, thrombolysis in myocardial infarction grade 3 flow was obtained as an optimal angiographic result in the RCA. Platelet counts were assessed daily and showed a stable trend. At the suggestion of the hematology department, the eltrombopag therapy was stopped. The patient was examined for an underlying hypercoagulable state. His homocysteine level was within normal limits. Antinuclear antibodies, antiphospholipid and anticardiolipin antibodies, lupus-like anticoagulant, and mutations of factor V Leiden were negative. The patient was discharged on the 5th day with a platelet count of 125,000/mL, with advice to continue dual anti-platelet therapy (acetylsalicylic acid 100 mg and clopidogrel 75 mg). There was no relapse for ITP during the 1-year follow-up period (Table 1).

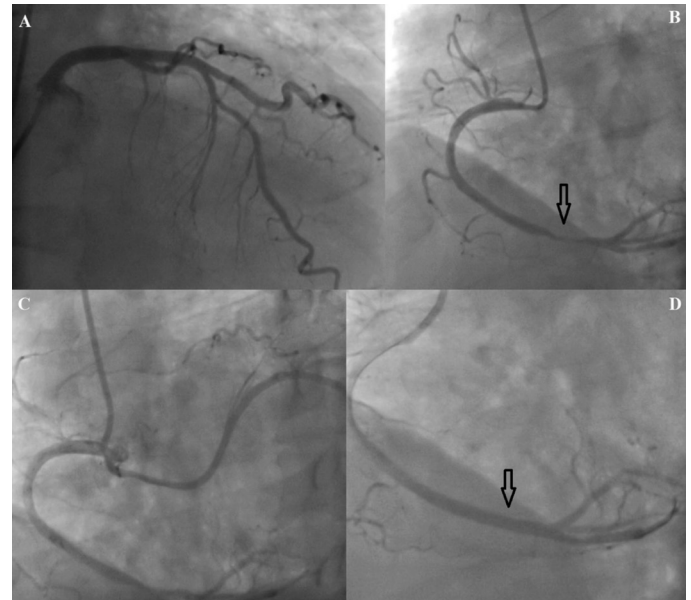


Figure 1. A) Non-critical plaque on the proximal and middle portion of the left anterior descending artery, B) arrow shows sub-total occlusion at the distal portion of the right coronary artery, C) circumflex coronary artery originates from the right aortic root, D) bare metal stent (3.0x20 mm) was implanted at the lesion site and post-dilatation was performed with a non-compliant balloon (3.5x15 mm).

Table 1. The relationship between medical treatments and platelet counts during follow-up periods.

Time	4 months ago	2 months ago	1 month ago	2 weeks ago	1 week ago	Admission to ED	5 days later	1 month later	6 months later	1 year later
Platelet Count	60,000	93,000	5000	13,000	105,000	107,000	125,000	105,000	272,000	292,000
Therapy	P-16 mg initiated	P-64 mg	E-50 mg initiated	E-50 mg	E-50 mg	E-50 mg	C-75 mg, ASA-100 mg	C-75 mg, ASA-100 mg	C-75 mg	C-75 mg
Events	Relapse	Follow-up	Newline therapy	Follow-up	Follow-up	Myocardial infarction	Discharge	Follow-up	Follow-up	Follow-up

P: Prednisolone; E: eltrombopag; C: clopidogrel; ASA: acetylsalicylic acid; ED: emergency department.

Eltrombopag is an orally available, small, non-peptide organic molecule that enhances platelet production by binding to and activating c-Mpl, the thrombopoietin receptor, on megakaryocytes and their progenitors [5]. The main issue in our case is that, as we mentioned the importance of evaluating risk factors, our patient had no risk factors for CAD and we recognized the coincidence between acute coronary syndrome and the beginning of a new agent of thrombopoietin receptor agonist (TPO-A) therapy. TPO-A therapy has important side effects including thromboembolic events [6,7,8]. A recent study demonstrated that an important percentage of ITP patients undergoing eltrombopag therapy achieve complete response after cessation of the therapy. There is no reliable marker for predicting this response so far [9].

Coexistence of ITP and CAD presents complex problems. The crucial point in handling these problems is a balance between hemorrhagic risk and prevention of thrombotic events. Although eltrombopag is more effective in the treatment of patients with ITP, clinicians should pay more attention to side effects including thrombotic events, as we demonstrated in our case report.

Keywords: Acute myocardial infarction, Immune thrombocytopenic purpura, Eltrombopag

Anahtar Sözcükler: Akut miyokard infarktüsü, İmmün trombositopenik purpura, Eltrombopag

Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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***Candida*-Related Immune Response Inflammatory Syndrome Treated with Adjuvant Corticosteroids and Review of the Pediatric Literature**

Adjuvan Kortikosteroid ile Tedavi Edilen *Candida*-İlişkili İmmün Yanıt Enflamatuvar Sendromu ve Pediatrik Literatür Derlemesi

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To the Editor,

Chronic disseminated candidiasis (CDC) is a potentially fatal complication observed in febrile neutropenia [1]. The diagnosis is usually made after neutrophil recovery and microbiological proof has been often negative [2]. Granulomatous histopathology, radiological lesions coincident with resolution of granulocytopenia, and rapid response to corticosteroids favors immune-mediated pathogenesis. Recently, CDC has been suggested to be related to Immune response inflammatory syndrome (IRIS), an exacerbated response to a preexisting antigenic stimulus in patients with rapid immune restoration [1,3]. IRIS has been mostly documented in HIV-infected patients with immune recovery after antiretroviral therapy [4]. Here, we present a case of *Candida*-related IRIS and review the current literature on children.

A male, aged 6 years and 7 months, with B-cell acute lymphoblastic leukemia was treated for presumed typhlitis with meropenem, teicoplanin, and amphotericin B during induction

therapy. Thoracoabdominal CT scans revealed hepatosteatoses/hepatomegaly. Fever subsided on the 2nd day. During steroid tapering and on the 8th day of antibiotics, the patient developed fever and abdominal pain with marked elevation of liver enzymes, predominantly of GGT. Bone marrow examination showed no evidence of blasts or hemophagocytosis and the blood count was normal. Control imaging showed typical widespread hepatic bull's eye lesions (Figure 1). The liver biopsy demonstrated granulomatous inflammation, but no fungus was detectable. According to European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria, the diagnosis was possible invasive fungal infection, most likely candidiasis. Reappearance of symptoms after neutrophil recovery indicated IRIS. We empirically administered dexamethasone for 14 days. Fever disappeared after 24 h and liver function tests improved in 1 week. He was discharged with oral voriconazole. During vincristine therapy, voriconazole was replaced with amphotericin B to avoid toxicity. In the 13th month of voriconazole, the liver lesions showed partial regression and calcification. As re-biopsy was negative for microorganisms and showed only rare microgranulomas, we stopped the voriconazole. The patient completed chemotherapy and has been without any exacerbation for 32 months since the initial diagnosis of IRIS.

Clinical and/or radiological deterioration after neutrophil recovery is a well-known entity in patients treated for opportunistic infections [4]. The immune system shifts towards Th-1 type response and amplifies proinflammatory cascades [1]. Therefore, the severity of radiological/clinical findings might depend on the immune status of the patient [5,6]. IRIS is a diagnosis of exclusion; other possible causes of persistent fever should be evaluated. If the clinical scenario is not consistent with preexisting disease, treatment side effects, or a possible newly acquired pathogen, IRIS deserves diagnostic consideration. In the previous *Candida*-related IRIS reports on children with cancer, all patients had fever and liver dysfunction accompanying normal neutrophil counts. Liver biopsies showed granuloma formation. Tissue cultures for fungi were negative in all samples except one. The

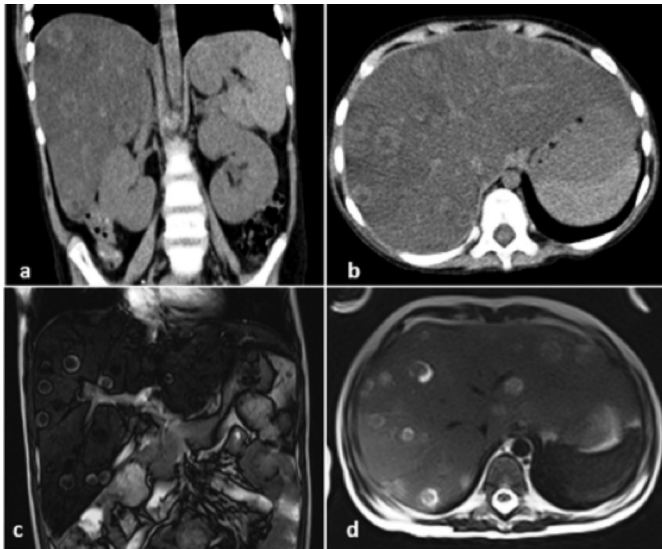


Figure 1. Coronal and axial computed tomography images (a, b); coronal and axial magnetic resonance images of circumscribed typical hepatic *Candida* lesions (c, d).

Table 1. Review of pediatric cases of *Candida*-related Immune response inflammatory syndrome treated with corticosteroids.

Authors	Age (years)	Diagnosis	Proof of <i>Candida</i>	ANC/mm ³	Biopsy	Liver Dysfunction	Antifungal Treatment	Steroid Dose and Duration	Outcome
Saint-Faust et al. [11]	12	AML	<i>Candida</i> antigen and serology (+)	2800	Granulomatous lesion, <i>Candida</i> (-)	(+)	AmB (1 mg/kg)	Pred 1 mg/kg, 60 days	Radiological improvement in 30 days. At 24 h, fever and pain disappeared and liver dysfunction improved.
Saint-Faust et al. [11]	8	ALL	<i>Candida</i> serology (+)	2580	Granulomatous lesion, <i>Candida</i> (-)	(+)	L-AmB (3 mg/kg)	Pred 1 mg/kg, 90 days	Fever and pain disappeared in 2 days. radiological improvement in 30 days.
De Castro et al. [10]	Median: 46 (2-76)	14 mixed	*	Unknown	Unknown	Mostly (+)	*	Mean: 1 mg/kg/day* Median: 1.5 (1-10 months)	*
Conter et al. [8]	17	Lymphoma	<i>Candida</i> serology (+)	12,000	Granulomatous lesion, pseudomycetia (+)	(+)	AmB (1 mg/kg)	Pred 1 mg/kg, 120 days	Fever disappeared in 24 h, clinical improvement in 7 days, radiological improvement in 6 weeks.
Legrand et al. [3]	Median: 18.6 (2-65)	10 hematological malignancies	Blood culture (+), 1/10; stool culture (+), 7/10; urine culture (+), 1/10	Median: 19,372	Yeast positive in smear (5/10), culture positive (1/10), granulomas	(+)	*	Median** 0.66 mg/kg/day (0.4-2) Median 109 (49-240 days)	Clinical improvement at median 4.5 days (1-30). Radiological improvement in 107 days (mean: 30-210 days).
Bayram et al. [7]	16 months	ALL	(-)	WBC: 36,100	(-)	(+)	Fluconazole, voriconazole	DXM 0.5 mg/kg, 14 days	Fever disappeared in 3 days, liver tests normalized in 7 days, USG findings normalized in 30 days.
Current case	6.5	ALL	(-)	2750	Granulomatous lesion, <i>Candida</i> (-)	(+)	L-AmB (3 mg/kg), then voriconazole	DXM 0.4 mg/kg, 14 days	Fever disappeared in 24 h, liver function tests improved in 1 week. Radiological improvement in 2 months.

*Case series studies, i.e. details unspecified. ALL: Acute lymphoblastic leukemia, ANC: absolute neutrophil count, AmB: amphotericin B, L-AmB: liposomal amphotericin B, Pred: prednisolone, DXM: dexamethasone, **: prednisone equivalent.

most commonly administered antifungal agent was amphotericin B. Details of steroid therapy and the outcomes are presented in Table 1 [3,7,8,9,10,11]. Increased susceptibility to infection might be a drawback for prolonged corticotherapy. However, neither *Candida* reactivation nor other new opportunistic infections have been reported [3].

Candida-related IRIS has been rarely reported in children. Early recognition and appropriate management of IRIS might prevent unnecessary diagnostic procedures, antibiotic usage, and chemotherapy delays.

Acknowledgment

This work was partially presented at the 9th Biennial Childhood Leukemia Symposium, Prague, Czech Republic, 28-29 April 2014.

Keywords: Leukemia, Febrile neutropenia, *Candida*, Immune response inflammatory syndrome

Anahtar Sözcükler: Lösemi, Febril nötropeni, *Candida*, İmmün yanıt enflamatuvar sendromu

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Posttranslational Modifications of Red Blood Cell Ghost Proteins as “Signatures” for Distinguishing between Low- and High-Risk Myelodysplastic Syndrome Patients

Düşük ve Yüksek Risk Miyelodisplastik Sendrom Hastalarını Ayıran “İşaretler” Olarak Kırmızı Kan Hücre Zarı Proteinlerinin Posttranslasyonel Modifikasyonları

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To the Editor,

Myelodysplastic syndrome (MDS) comprises a heterogenic group of oncohematological diseases that affect hematopoiesis. Although the precise cause of MDS is unknown, multiple factors are involved, one of the most widely implicated of which is

oxidative stress. However, it is unclear whether oxidative stress is a cause of MDS or an effect of other pathological mechanisms.

Red blood cells (RBCs) are the first cells exposed to stress stimuli. They are highly vulnerable to free radical accumulation, which leads to the oxidative stress that induces damage in proteins and

other biomacromolecules [1]. In MDS, the RBC proteome can be affected by effects of the peripheral blood environment and/or by abnormal processes possibly caused by oxidative stress during hematopoiesis in bone marrow. Therefore, we chose red cell membranes (ghosts) as a model biological material.

Patient characteristics are summarized in Table 1. All individuals tested agreed to participate in the study on the basis of informed consent. All samples were obtained and analyzed in accordance with the Ethics Committee regulations of the Institute of Hematology and Blood Transfusion. The RBCs were isolated from whole blood by differential centrifugation and frozen at -80 °C. The red cell ghosts were isolated according to the method of Dodge et al. [2]. Proteins were separated using 2D SDS-PAGE followed by silver staining [3]. The gels were digitized and processed using Progenesis SameSpots software. Significantly differing spots ($p < 0.05$) were submitted for protein identification by tandem mass spectrometry coupled to a Nano LC system.

By comparing the high- and low-risk MDS ghost proteomes, we found 22 significantly differing spots that corresponded to 16 unique proteins, particularly spectrin and its interaction partners in the membrane skeleton meshwork (actin, tropomodulin, tropomyosin, ankyrin, protein 4.1). To determine whether the changes were caused by protein expression level alterations or by posttranslational modifications, we analyzed the LC-MS data using Progenesis LC-MS software. No significant changes in

protein expression levels were observed. Therefore, the changes between the low- and high-risk MDS cohorts were caused by protein modifications.

It is well known that RBC function may be radically affected by membrane protein posttranslational modifications. For example, the increased phosphorylation of spectrin, the protein crucial for cytoskeletal stability, worsens the mechanical properties of the RBC membrane [4], and the phosphorylation of protein 4.1 leads to RBC osmotic fragility. Moreover, increased protein 4.1 mobility, suggesting the presence of other modifications, has been observed in MDS patients. The production of abnormal protein 4.1 may result in the dysregulation of spectrin-actin interaction and may cause both RBC shape change and membrane instability [5]. In addition, altered membrane morphology, including holes and thorn-like structures, was described for the RBCs of MDS and acute myeloid leukemia patients [6].

Because the impact of RBC protein modifications is clear, our preliminary data suggest that it might be possible to profile MDS patients according to the type of modification. Such modifications could thus be considered characteristic signatures of MDS or its progression. As such, they might help in the earlier diagnosis and treatment of MDS patients.

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Contributors' Statement

KP and PM performed research. KP, PM, JC, and JED designed the study. JC provided samples. KP, PM, JC, and JED drafted the manuscript. All authors read and approved the final manuscript.

Keywords: Myelodysplastic syndromes, Proteomics, Red blood cell ghosts, Posttranslational modifications, Erythrocytes, Electrophoresis

Anahtar Sözcükler: Miyelodisplastik sendrom, Proteomik, Kırmızı kan hücre zarı, Posttranslasyonel modifikasyon, Eritrosit, Elektroforez

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Risk	Sample	Diagnosis	Sex	Sex (%)	Age (years)	Median age
Low risk	1	RCMD	F	40	41	61
	2	RARS	F		59	
	3	RCMD	F		57	
	4	RCMD	F		64	
	5	RARS	M	60	62	
	6	RA	M		79	
	7	RCMD	M		51	
	8	RCMD	M		75	
	9	RARS	M		40	
	10	RCMD	M		67	
High risk	11	RAEB-1	F	67	58	63
	12	RAEB-2	F		65	
	13	RAEB-2	F		67	
	14	RAEB-2	F		63	
	15	RAEB-2	M	33	55	
	16	RAEB-1	M		67	

RCMD: Refractory anemia with multilineage dysplasia, RARS: refractory anemia with ringed sideroblasts, RA: refractory anemia, RAEB-1: refractory anemia with excess of blasts type 1, RAEB-2: refractory anemia with excess of blasts type 2, F: Female, M: Male.

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Intradiploic Hematoma in a Hemophilic Patient: Hemophilic Pseudotumor of Calvarium

Hemofilik Bir Hastada Intradiploik Hematom: Kraniyumun Hemofilik Psödotümörü

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To the Editor,

Pseudotumors are results of repeated hemorrhage into soft tissues, the subperiosteum, or a site of bone fracture with inadequate resorption of the extravasated blood. We describe a patient with a huge hemophilic pseudotumor of calvarium, which occurs very rarely.

A 14-year-old boy with mild hemophilia A (FVIII coagulant activity: 5.8%) without inhibitor presented with epileptic seizure 7 years ago. The patient was known to be hemophilic from birth after a birth injury and brain damage had occurred. He was mentally retarded and had habitual head-hitting behavior. His family noticed progressively enlarging painless scalp swelling on his head.

There was obvious asymmetry of the head and face (Figure 1, A-3). His neurological examination was normal and radiological investigations did not reveal any other pathology. A computed tomography (CT) scan showed a large lesion with a mass effect over the underlying brain (Figure 1, A-1 and A-2).

Surgery was carried out with coagulation factor replacement (FVIII). During surgery a skin flap was done and the thinned outer table was incised (Figure 1, B-1). Mud-like material and a liquefied clot were evacuated (Figure 1, B-2). The thin and elastic inner wall was not removed to avoid postoperative complications (Figure 1, B-3).

Following surgery, antiepileptic medication was continued and short-term prophylaxis (30 IU/kg, three times a week) was applied for 8 weeks. At the 7-year follow-up of the patient, he was free

of seizures and a CT scan of the patient showed that acceptable calvarial remodeling had occurred (Figure 1, C-1 and C-2).

Proximal pseudotumors may destroy the soft tissues, erode the bone, and cause serious vascular and/or nerve damage [1].

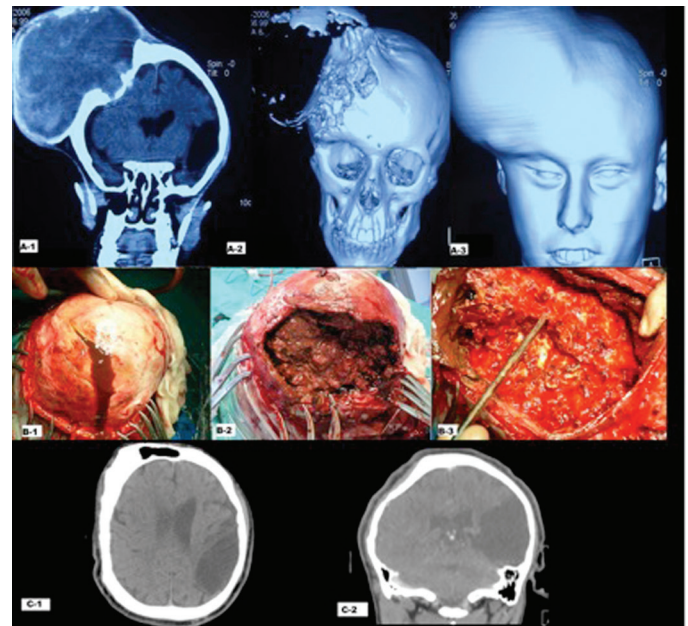


Figure 1. A-1, A-2, A-3: Multidetector computed tomography scan with reconstruction shows large lytic intradiploic lesion with expansion and scalloping of the bony margins; please note that the inner and outer tables are separated and destroyed. B-1, B-2, B-3: Intraoperative images; evacuated lesion was mud-like, inner table was protected. C-1, C-2: Sagittal and coronal computed tomography images after 7 years; good and acceptable remodeling of the calvarium is seen.

Reduction of the pseudotumor and chronic joint disease is achieved by prophylactic treatment in severe hemophilia.

Calvarial localization of a pseudotumor is unusual [2]. Inflammation due to hematoma causes immune reaction and affects nearby tissues. The skull tables provide natural protection from soft tissues being eroded [3]. All intradiploic lesions should be suspected to be hematomas unless proven otherwise in patients with coagulopathies [2].

Total surgical removal of the hematoma is the treatment of choice. Some authors recommend cosmetic cranioplasty within the same surgical procedure [4]. However, most of them prefer to preserve the intact inner table [5]. According to us, the elastic inner table must be preserved to avoid postoperative complications. Acceptable bone remodeling was seen in the seventh year of follow-up in control CT images. However, a noncompressible inner table must be excised.

In summary, intradiploic hematoma must be expected when an intradiploic lesion is seen with hemophilia. The main part of the surgery is the preservation of the inner table of the cranium in hemophilic patients. Bone remodeling gives good results with time.

Keywords: Hemophilia A, Intradiploic hematoma, Coagulopathy, Intraosseous

Anahtar Sözcükler: Hemofili A, İntradiploik hematoma, Koagülopati, İntraosseoz

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The Second and Third Hemoglobin Kansas Cases in the Turkish Population

Türk Popülasyonundaki İkinci ve Üçüncü Hemoglobin Kansas Olguları

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To the Editor,

We read with great interest the article by Keser et al. [1] regarding the first observation of hemoglobin Kansas in Turkey. The authors described a patient from Malatya as the first case of hemoglobin Kansas in the Turkish population. After the publication of this paper, we had two other hemoglobin Kansas cases from the Malatya region.

Case 1: A 16-year-old female patient was admitted with the

complaint of cyanosis of her lips and nails since birth, but she had no problems in her daily life. In her family history, there were other relatives who had the same complaints (Figure 1a). Physical examination of our patient indicated slight cyanosis of her lips, nail beds, and skin (Figure 2). Other system examinations were normal. Transcutaneous oxygen saturation was detected as 50%. Her complete blood count, electrocardiogram, echocardiogram, methemoglobin level, and peripheral blood smear were normal. In blood gas values, pH was 7.39, PCO₂ was 41.1 mmHg, PO₂ was 66.3 mmHg, and the P50 value was 66.94 (normal value: 24-

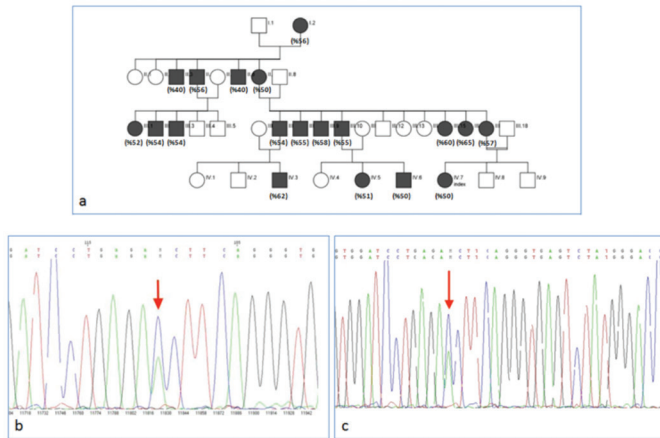


Figure 1. a) Family tree of the patients (transcutaneous oxygen saturations of the affected individuals are shown in parentheses); b) hemoglobin Kansas in DNA sequencing of case 1; c) hemoglobin Kansas in DNA sequencing of case 2.

29). Hemoglobin electrophoresis revealed HbA1 of 56.3%, HbA2 of 43.5%, and HbF of 2%. In beta-globulin gene DNA sequence analysis, c.308 A>C (β 102(G4) Asn>Thr) (Hb Kansas) mutation was detected (Figure 1b).

Case 2: A 43-year-old patient, the mother of Case 1, was admitted with the same complaints as her daughter. Transcutaneous oxygen saturation showed low oxygen levels (PO₂ 57%). Complete blood count, blood chemistry, and cardiac echocardiography were within normal limits. High-performance liquid chromatography results were as follows: HbA1 57.2%, HbA2 42.5%, HbF 0.2%. DNA sequencing revealed the same A to C substitution at nucleotide position 308 as in the first case (Figure 1c).

Hemoglobin Kansas is a rare, unstable, abnormal hemoglobin variant with low oxygen affinity in which asparagine is replaced with threonine in the 102nd position of the β -globin chain [2,3]. In these patients, hemoglobin leaves more than the normal amount of oxygen to extrapulmonary tissues. Therefore, tissues get oxygenated even at low hematocrit levels and patients appear to be healthy. However, cyanosis is seen because the unsaturated hemoglobin amount in the capillaries and veins is higher than 5 g/dL [4]. The P50 values of these patients are also high [5,6].

In total, six hemoglobin Kansas cases were reported from 1968 to date in the world literature [2,3,4,5]. The first hemoglobin Kansas case in Turkey was reported in 2015 [1]. Our patients and 17 other family members who had the same phenotype are more than all of the reported cases in the world literature. We could not perform hemoglobin electrophoresis and genetic evaluations of the other 17 family members because they were living in other



Figure 2. A photograph of case 1 showing cyanosis of her lips.

cities. However, these patients had low transcutaneous oxygen saturations, as shown in parentheses in Figure 1a. Hemoglobin Kansas and other unstable hemoglobinopathies with low oxygen affinity should be considered in the differential diagnosis of patients with unexplained peripheral cyanosis.

Keywords: Abnormal hemoglobins, Hb Kansas

Anahtar Sözcükler: Anormal hemoglobinler, Hb Kansas

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Leukocytoclastic Vasculitis Associated with a New Anticoagulant: Rivaroxaban

Yeni bir Antikoagülanla İlişkili Lökositoklastik Vaskülit: Rivaroksaban

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To the Editor,

Rivaroxaban, an oral direct factor Xa inhibitor, is one of the non-vitamin K antagonist anticoagulants and has been approved for various thrombotic diseases. Here we present a patient who developed leukocytoclastic vasculitis (LCV) associated with rivaroxaban as a rare non-bleeding side effect.

A 28-year-old man who was being treated with diltiazem (60 mg/day) and oral methylprednisolone (32 mg on alternate days) (6th month of Pozzi protocol [1]) for IgA nephropathy was admitted to our hospital with bilateral lower extremity non-blanching palpable purpura that occurred 10 days following the addition of 20 mg of rivaroxaban once daily for acute deep venous thrombosis in the right popliteal vein by another physician. There was no significant finding in the physical examination except for purpura. The complete blood count, metabolic panel, urine analysis, coagulation studies, infectious serologies, rheumatologic work-up, and serum immunoglobulin E level were all within normal limits. Rivaroxaban was replaced with subcutaneous enoxaparin sodium at 6000 IU twice a day, and the skin lesions disappeared within 1 week. Two weeks later, the patient was prescribed rivaroxaban at 10 mg a day again by the same physician who was following the patient for deep venous thrombosis because of the rarity of LCV due to rivaroxaban in the literature. Bilateral lower extremity purpura (Figure 1) reoccurred within 3 days of retreatment and a skin biopsy revealed neutrophil-predominant infiltrations within and surrounding the dermal small vessels, nuclear dust, vessel wall damage, erythrocyte extravasation, and fibrin deposition concurrent with vasculitis. Rivaroxaban was discontinued and enoxaparin was administered again, and the skin lesions resolved. The patient was in a clinically steady state for IgA nephropathy during the two episodes of vasculitis.

LCV is associated with the deposition of the immune complex in small vessels that brings about loss of vessel wall integrity and extravasation of erythrocytes by immune response resulting in purpura. Although drugs and infections are the most common etiologies for LCV, idiopathic forms of the disease account for approximately half of all cases [2]. Connective tissue diseases, other systemic diseases, and hematologic or solid organ malignancies are other remaining causes of LCV [3]. The interval between

administration of the suspected agent and the onset of symptoms is variable, symptoms mostly occur 7 to 10 days after exposure. Treatment of LCV starts with cessation of the causative drug and palliation of symptoms after systemic involvement is excluded. Systemic therapies such as colchicine, dapsone, corticosteroids, and some other immunosuppressive medications are used for managing serious and refractory disease [3,4].

There is only one similar report in the literature, from Chaaya et al., in which they presented a 68-year-old male patient with multiple comorbidities who developed signs of LCV after 7 days of rivaroxaban treatment due to deep venous thrombosis [5]. In that report, the findings of LCV disappeared within 1 week following the discontinuation of rivaroxaban and allopurinol plus a short course of intravenous methylprednisolone.

In conclusion, this report is the second case of rivaroxaban-associated LCV in the literature and this adverse event should be included in the list of significant adverse reactions to rivaroxaban.



Figure 1. Non-blanching palpable purpura is seen on the right lower leg.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Keywords: Vasculitis, Anticoagulants, Rivaroxaban

Anahtar Sözcükler: Vaskülit, Antikoagülan, Rivaroksaban

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