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CONTENTS

JEURMEDS

J Eur Med Sci 2025;6;(2):23-25

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Letter to the Editor

23

Pemphigus Vulgaris Developing During IVF (*In Vitro* Fertilization) Treatment: A Case Report

IVF (In vitro Fertilizasyon) Tedavisi Sırasında Gelişen Pemfigus Vulgaris: Bir Olgu Raporu

Kübra KARATAŞ, Sibel YILDIZ, Selami Aykut TEMİZ, İlkay ÖZER, Munise DAYE, Recep DURSUN

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Dear Editor,

A 24-year-old female patient presented to our outpatient clinic with progressively worsening painful erosions affecting the oral, genital, and cutaneous regions. She had no prior history of pemphigus and was 10 weeks pregnant, receiving progesterone treatment (vaginal suppository and intramuscular injection). It was noted that her lesions had started approximately three months earlier, coinciding with her *in vitro* fertilization (IVF) treatment for primary infertility. During the onset of the lesions, she underwent ovarian stimulation with follitropin alfa and estradiol as part of the IVF protocol, but embryo transfer was not performed. Nevertheless, she subsequently achieved a successful pregnancy and presented to our clinic at 10 weeks of gestation.

Dermatological examination revealed widespread erosions and remnants of bullae on the oral, genital, and anal mucosa; hemorrhagic crusted erosions on the lips; and scattered bullae with crusted erosions on the skin (Figures 1, 2, and 3). The Nikolsky sign was positive. Based on clinical findings, pemphigus vulgaris was suspected. Histopathological and direct immunofluorescence analyses confirmed the diagnosis. Indirect immunofluorescence revealed high titers of anti-desmoglein 1 and 3 antibodies (>200 RU/mL). Following consultation with obstetrics and gynecology, topical corticosteroids and systemic methylprednisolone (0.5 mg/kg/day) were initiated, and progesterone therapy was discontinued. After the consolidation phase, systemic corticosteroids were gradually tapered by 20% every two weeks and discontinued within approximately four months. The patient showed a favorable response to treatment, with regression of existing lesions and no emergence of new ones. Routine antenatal evaluations revealed no

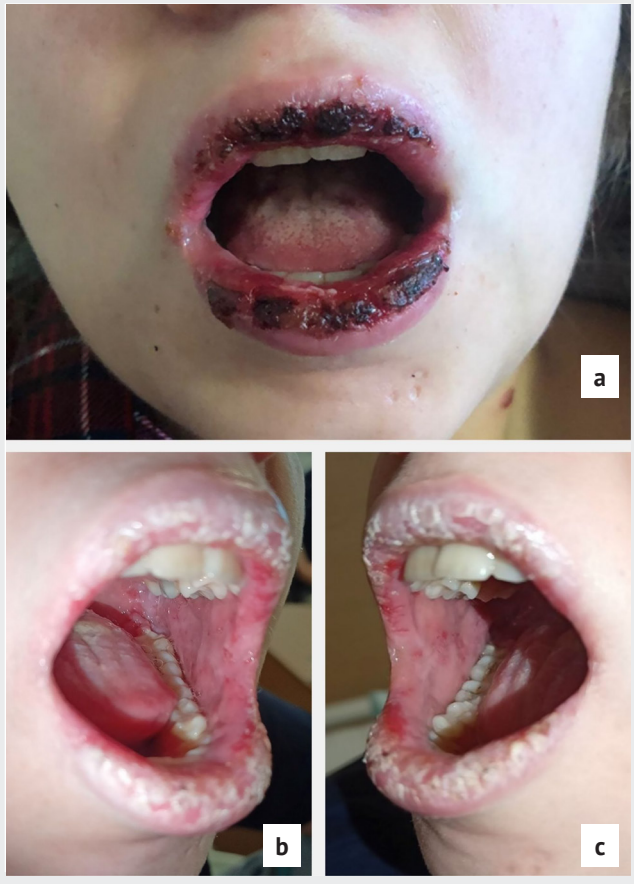

Figure 1. Clinical findings of the oral mucosa and lips. (a) Hemorrhagic crusty erosions on the lips, (b) erosions on the oral mucosa (right buccal region), (c) erosions on the oral mucosa (left buccal region)

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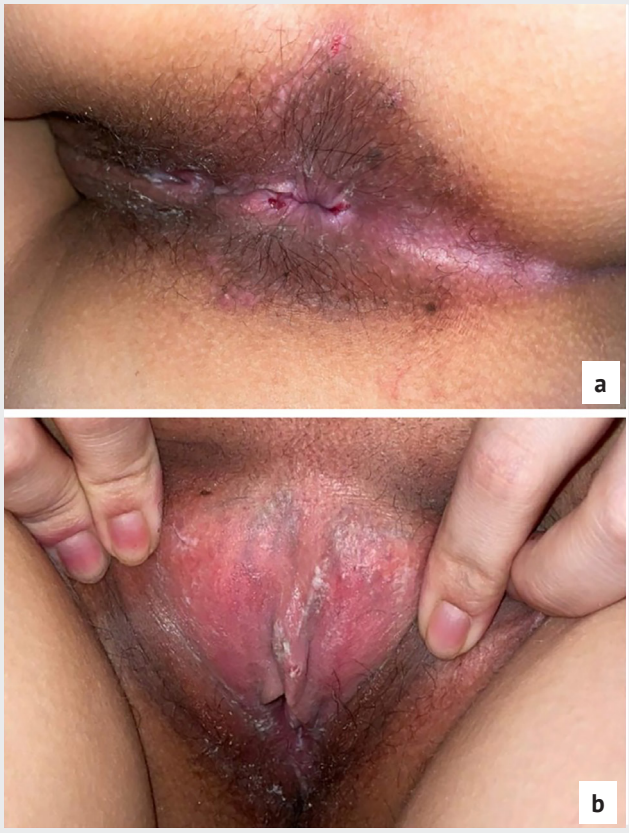

Figure 2. Mucosal erosions involving the anogenital region. (a) Erosions on the anal and perianal mucosa, (b) erosions on the genital mucosa

abnormalities. However, immediately postpartum, widespread mucocutaneous erosions recurred, which were effectively controlled with a moderate dose of systemic steroids (0.5 mg/kg/day). No neonatal pemphigus was observed.

Pemphigus vulgaris is a Th2-mediated autoimmune bullous disease, primarily driven by anti-desmoglein autoantibodies. Although the association between pregnancy and pemphigus vulgaris remains incompletely understood, hormone-induced immune modulation has been implicated in its pathogenesis. Elevated levels of estrogen and progesterone during pregnancy shift the immune response from a Th1- to a Th2-dominant profile. While this physiological shift promotes fetal tolerance, it may also predispose individuals to autoantibody-mediated diseases such as pemphigus vulgaris (1,2). Similarly, the hormonal agents used in IVF treatment may contribute to this immunological imbalance.

Following delivery, the abrupt decline in estrogen and progesterone levels induces a reversion to a Th1-dominant immune response. This transition leads to immune remodeling and can facilitate postpartum exacerbations of autoimmune diseases (1,2). Furthermore, the withdrawal of endogenous corticosteroids, previously produced by the chorion, may also contribute to postpartum flare-ups (3).

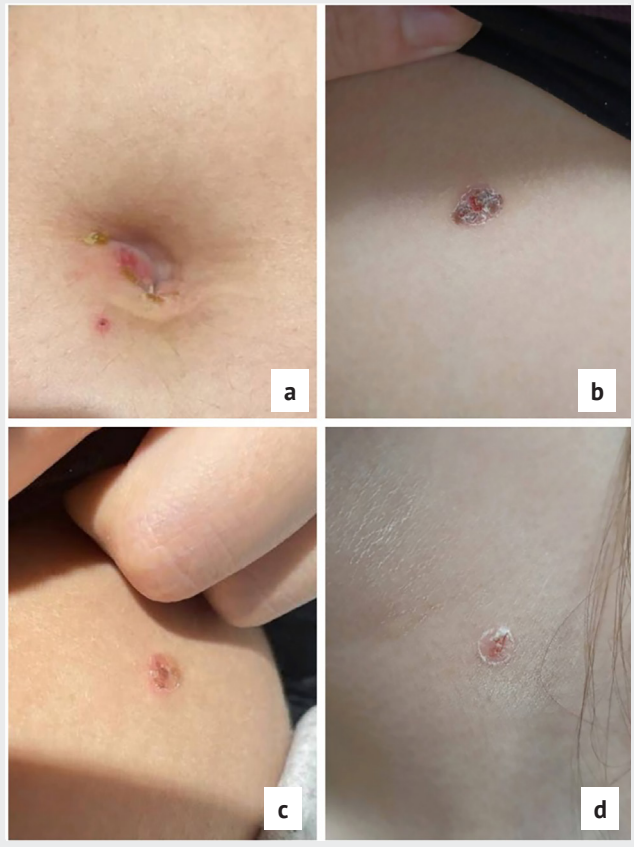

Figure 3. Cutaneous lesions on different body sites. (a) Bullae and erosions on the abdomen, (b) crusted erosions on the back, (c) erosions with bullae on the abdomen, (d) crust formation and healing erosions on the neck

To date, only one similar case has been reported in the literature. In the case presented by Gayathri Devi et al. (4), a 28-year-old woman developed pemphigus vulgaris following IVF-confirmed pregnancy. Exogenous hormone therapy was considered the likely trigger, and the patient responded well to systemic corticosteroids.

Both cases suggest that pemphigus vulgaris is a rare but possible complication of IVF treatment. Our case differs from the previously reported one in that the lesions developed before embryo transfer, during the hormonal stimulation phase alone. This supports the hypothesis that exogenous hormones may trigger pemphigus vulgaris independently of pregnancy. Additionally, our case is notable due to its postpartum relapse, which presents uncommon characteristics in the context of the patient's medical history.

Pemphigus vulgaris during pregnancy may lead to serious maternal and fetal complications (3,5). The condition complicates clinical management and may affect treatment decisions and prognosis. Systemic corticosteroids remain the first-line treatment during pregnancy owing to their relatively favorable safety profile and classification as

pregnancy category C. In corticosteroid-resistant cases, intravenous immunoglobulin is the preferred second-line option. Plasmapheresis has also been reported to be effective and safe in refractory cases. However, further studies are required to validate the safety and efficacy of these alternative therapies. Azathioprine, classified as category D, is associated with congenital anomalies and preterm birth. Methotrexate, cyclophosphamide, and mycophenolate mofetil are teratogenic and contraindicated during pregnancy. Rituximab is classified as pregnancy category C, with limited data on safety, and poses a risk of B-cell depletion in neonates. (1,6,7). Management should be individualized through a multidisciplinary approach, considering factors such as gestational age, maternal condition, fetal development, and potential treatment-related risks.

In conclusion, our case highlights that hormonal changes related to IVF treatment may trigger pemphigus vulgaris. Both endogenous and exogenous hormonal stimulation may contribute to the initiation or exacerbation of autoimmune processes. Particular attention should be paid to individuals undergoing infertility treatments. Timely diagnosis and carefully tailored treatment strategies are essential in managing pemphigus vulgaris during pregnancy. This case demonstrates that systemic steroid therapy can elicit a positive response, and appropriately individualized treatment plans may lead to successful outcomes for both the mother and the fetus. Early recognition and appropriate intervention are crucial to prevent complications in both the mother and fetus.

Informed Consent: Patient consent was obtained.

Footnotes

Authorship Contributions

Concept: K.K., S.Y., S.A.T., Design: K.K., S.Y., S.A.T., Literature Search: K.K., S.Y., S.A.T., Writing: K.K., S.Y., S.A.T., İ.Ö., M.D., R.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Frequency of Anemia in Critically Ill Patients Admitted to the Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Ünitesine Kabul Edilen Kritik Hastalarda Anemi Sıklığı

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ABSTRACT

Objective: Although anemia is known to be common in patients admitted to and followed up in the pediatric intensive care unit (PICU), our knowledge regarding the pre-intensive care period is limited. This study was conducted to investigate the frequency of anemia in critically ill children admitted to the PICU.

Material and Methods: During the study period between 15 November 2023 and 15 March 2024, the sex, age, acute and/or chronic diseases, reason for admission, complete blood count, and C-reactive protein (CRP) results obtained within 24 hours before or at the time of admission of the patients admitted to the intensive care unit were recorded from the hospital computer management system.

Results: Total of n=292 patients were admitted to the intensive care unit. According to the exclusion criteria, n=87 patients were excluded from the study. Of the 205 patients included, 58.5% were male, with a mean age of 74.34±66.66 months. The incidence of anemia was found to be 59%. It was observed that 30.2% of anemia was normocytic, and 25.9% was microcytic. Normocytic anemia was the most common type in all age groups except for 7-24 months, in which microcytic anemia was more frequent. Anemia most frequently accompanied acute infections, hemato-oncologic diseases, and chronic illnesses, and was of the normocytic type. Red cell distribution width (RDW) was elevated in 65.4% of patients. In patients without anemia, RDW was normal, whereas in microcytic and normocytic anemia, it was high and associated with elevated CRP, acute infection, hemato-oncologic, and chronic diseases.

Conclusion: Anemia is a finding requiring specific evaluation according to the patient's age and health status. Since critically ill children have a low capacity to tolerate anemia, their blood count values should be monitored regularly during and after admission. Comprehensive studies are needed to investigate whether RDW may serve as a marker of inflammation in critically ill children.

Keywords: Anemia, critically ill child, pediatric intensive care, incidence

ÖZ

Giriş: Aneminin çocuk yoğun bakıma kabul edilen ve takip edilen hastalarda sık olduğu bilinmesine karşın yoğun bakım öncesi dönem konusundaki bilgilerimiz kısıtlıdır. Bu çalışma çocuk yoğun bakım ünitesine (YBÜ) kabul edilen kritik hasta çocuklarda anemi sıklığını araştırmak amacıyla yapılmıştır.

Gereç ve Yöntemler: Çalışma aralığı olan 15 Kasım 2023 ve 15 Mart 2024 arasında YBÜ kabul edilen hastaların cinsiyeti, yaşı, akut ve/veya kronik hastalıkları, üniteye yatış nedeni, yatışından önceki 24 saat içerisinde veya yatış sırasında alınmış olan tam kan sayımı, C-reactive protein (CRP) sonuçları hastane bilgisayar yönetim sisteminden kayıt edilmiştir.

Bulgular: 15 Kasım 2023 ve 15 Mart 2024 arasında yoğun bakım ünitesine toplam n=292 hasta yatışı olmuştur. Çalışma dışı bırakma kriterlerine göre n=87 hasta çalışma dışı bırakılmıştır. Çalışmaya dahil edilen 205 hastanın %58,5'i erkek, yaş ortalaması: 74,34±66,66 ay'dır. Anemi insidansı %59 bulunmuştur. Aneminin %30,2 normositik, %25,9 mikrositik olduğu görülmüştür. Normositik anemi 7-24 ay hariç tüm yaş gruplarında en sık görülen anemi şeklidir. Yedi-24 ay arasında mikrositik anemi daha fazla görülmüştür. Anemi en sık akut enfeksiyon, hematoonkolojik hastalık ve kronik hastalıklara eşlik etmektedir ve normositik tiptedir. Hastaların %65,4'ünde kırmızı kan hücrelerinin (RDW) yüksek olduğu gözlenmiştir. Anemi saptanmayan hastalarda RDW normal iken mikrositik ve normositik anemi, CRP yüksekliği, akut enfeksiyon, hematoonkolojik hastalıklar ve kronik hastalıklar ile ilişkili ve yüksek bulunmuştur.

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ÖZ

Sonuç: Anemi hastanın yaş ve sağlık durumuna göre özel değerlendirme gerektiren bir belirtidir. Kritik hasta çocukların anemiyi tolere etme kapasitesinin düşük olması nedeniyle hastaların kan sayımı değerleri kabul sırasında ve sonrasında düzenli olarak takip edilmelidir. Kritik hasta çocuklarda RDW'nin enflamasyon göstergesi olabileceği konusunda geniş katılımlı çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Anemi, kritik çocuk hasta, çocuk yoğun bakım, sıklık

INTRODUCTION

Anemia is defined as a decrease in hemoglobin (HGB), hematocrit levels, and erythrocyte count below two standard deviations according to age and sex (1,2). Anemia is a common and serious problem in the pediatric intensive care unit (PICU) (3). It is known that one-third of critically ill children hospitalized in the PICU for at least two days are anemic at admission, and 40% develop anemia during their stay (4). In critically ill children, chronic anemia, acute or chronic blood loss, underlying diseases, bone marrow-suppressing treatments, and insufficient erythropoietin response contribute to anemia development. In these patients, anemia reduces the oxygen-carrying capacity of the blood and causes tissue and organ failure. Critically ill children with low baseline HGB levels have been shown to require multiple transfusions, prolonged intensive care stay, and more inotropes, invasive mechanical ventilation and extracorporeal therapy (5,6). Although anemia is common in critically ill patients, it is an important finding often overlooked in daily medical practice. The balance between avoiding unnecessary transfusions and tolerating anemia depends on understanding the complex etiology of anemia. Using HGB levels in transfusion decisions is the most common practice. The TAXI and TRIPICU guidelines provide transfusion recommendations based on HGB levels. However, in different clinical conditions such as sepsis, shock, congenital heart disease, and trauma, these guidelines emphasize that the patient's clinical findings should also be considered when deciding whether to monitor anemia or increase HGB levels (7,8). Although anemia is known to be frequent in patients admitted to and followed up in the intensive care unit, information regarding the pre-intensive care period is limited. The aim of this study was to investigate the frequency of anemia in critically ill children admitted to the PICU.

MATERIALS and METHODS

The study was conducted within the framework of the Basic Competency Course, which aimed to provide fourth-year students of Adana Faculty of Medicine during the 2023-2024 academic year with instruction on the planning, execution, and completion of a research project, in collaboration with the student researchers. During the study period between 15 November 2023 and 15 March 2024, the student researchers made regular visits to the intensive care unit. The sex, age, acute and/or chronic diseases, reason for admission to the unit, and complete blood count and C-reactive protein (CRP) results obtained within the 24 hours before admission or at the time of admission were recorded from the hospital computer management system.

Inclusion of Patients in the Study

Patients followed for more than 48 hours in the PICU, aged between 1 and 216 months, whose admission data and blood test results were available, were classified into seven groups according to their reason for admission:

Infection: Acute infectious diseases such as encephalitis, acute lower respiratory tract infection, hepatitis, sepsis.

Hemato-oncological Diseases: Hematological diseases such as leukemia, hemophagocytic syndrome, and solid tumors.

Chronic Diseases: Chronic cardiac, renal, respiratory, and rheumatologic diseases.

Bleeding/trauma: Patients with acute blood loss such as from traffic accidents or trauma, who were not operated on and did not receive transfusion.

Epilepsy and Mental-Motor Retardation: Epileptic diseases accompanied by antiepileptic drug use and mental-motor retardation.

Metabolic Diseases: Metabolic conditions such as organic acidemia, maple syrup urine disease, acute gastroenteritis, diabetic ketoacidosis.

Postoperative/post-arrest: Postoperative patients who underwent elective surgeries such as gastrostomy placement, scoliosis, kyphosis operations, and patients with a history of out-of-hospital cardiac arrest.

To determine normal values for HGB, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean MCH, red cell distribution width (RDW), leukocyte, and platelet counts according to age group and sex, the Turkish Society of Hematology Complete Blood Count Guide was used (9). CRP values above 5 mg/L were considered elevated.

Exclusion criteria for the patients:

- Patients followed in the PICU for less than 48 hours,
- Patients whose blood results could not be obtained due to clotting or insufficient sample,
- Patients admitted to the unit after surgical intervention for acute blood loss,
- Patients admitted to the unit after receiving a blood transfusion in the inpatient ward or emergency department,
- Patients transferred to the ward but readmitted to the PICU within 24 hours for any reason.

Ethical approval for the study was obtained from the University of Health Sciences Türkiye, Adana City Training

and Research Hospital Clinical Research Ethics Committee (decision no: 2938, date: 09.11.2023).

Families of the patients included in the study were informed about the study and informed consent was obtained.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 20.0; Chicago, IL) software. Following distribution analysis, continuous variables were presented as mean ± standard deviation (minimum-maximum), while categorical data were expressed as numbers and percentages. For the analysis of two different categorical variables, contingency tables and the Pearson chi-square test were applied. A p value <0.05 was considered statistically significant.

RESULTS

During the study period between 15 November 2023 and 15 March 2024, a total of n=292 patients were admitted to the intensive care unit. According to the exclusion criteria, n=87 patients were excluded from the study. Among the 205 patients included in the study, 58.5% (120/205) were male, and the mean age was 74.34±66.66 months.

The incidence of anemia among patients admitted to the PICU was 59%, and it was observed that 30.2% of the anemia cases were normocytic and 25.9% were microcytic. No significant difference was found between patients with and without anemia in terms of sex and reason for admission. A significant relationship was identified between age groups and types of anemia. Normocytic anemia was the most common type of anemia in all age groups except for the 7-24-month group. Microcytic anemia was more frequently observed in the 7-24-month age group. The age of patients without anemia was higher than that of patients with anemia. Anemia was most frequently accompanied by acute infections, hemato-oncological diseases, and chronic diseases, and was of the normocytic type (Tables 1 and 2).

The CRP level was elevated in 50.8% of patients, and no relationship was found between CRP and anemia. It was observed that 65.4% of the patients had elevated RDW. While RDW was normal in patients without anemia, it was found to be elevated in patients with microcytic and normocytic anemia. Although not statistically significant, RDW was found to be elevated in patients most frequently admitted to the intensive care unit and diagnosed with normocytic anemia. In the 7-24-month group, RDW elevation accompanied microcytic anemia, whereas in the 0-6-month and 25-72-month groups, RDW elevation accompanied normocytic anemia.

DISCUSSION

Critically ill children are at high risk of anemia during and after their stay in intensive care. It is known that 33% of patients admitted to the PICU have anemia at the time of admission, 41% develop anemia during hospitalization, and 74% require transfusion. Patients requiring transfusion are known to be younger, to have higher PRISM mortality scores, and to have lower HGB values at the time of admission (4,10,11). In this study, the frequency of anemia among patients admitted to the PICU was found to be 59%. Although normocytic anemia was the most common type detected, there was a significant relationship between age and MCV. Accordingly, microcytic anemia was more frequent in the 7-24-month group, while normocytic anemia was more common in the 0-6-month and 25-72-month groups. The frequency of anemia decreased with increasing age. Nutritional deficiencies may be the cause of this result. It has been reported previously that 9% of intensive care patients have iron deficiency, and 2% have vitamin B12 and folate deficiency (12). Nevertheless, our knowledge regarding the relationship between nutritional anemia and critical illness in critically ill children remains limited. Anemia in patients admitted to the intensive care unit is multifactorial, and etiological investigations should be performed before transfusion and managed appropriately.

In children, an MCV value within the normal range for age indicates normocytic anemia. A high reticulocyte level in the presence of anemia is usually associated with hemolysis. In contrast, a normal or low reticulocyte level despite the presence of anemia indicates bone marrow insufficiency and is commonly seen in critically ill patients. Acute blood loss, early stage of acute hemolysis, acute inflammatory diseases, malignancy, renal, rheumatologic, and other chronic diseases, heart failure, chronic lung disease, ulcerative colitis, Crohn's disease, and celiac disease are causes of normocytic anemia with normal reticulocyte counts (13,14). In our patients, normocytic anemia is frequently observed in association with acute infections, hemato-oncological diseases, and chronic diseases. This result is expected in critically ill patients. In children, especially during infections accompanied by inflammation, decreased erythropoiesis, abnormal iron metabolism, and reduced erythropoietin production and response lead to a reduction in HGB levels. This condition is associated with suppression of iron metabolism due to increased hepcidin as a defensive response of immune cells. In addition, bone marrow suppression caused by infectious agents, administered treatments, and accompanying hemolytic processes contribute to the development of anemia (15,16). However, unlike previous studies, in our patients, RDW

Table 1. Anemia situation of patients according to sex, age groups and admission reason

	Non-anemic patients *n=84 (41%)		Anemic patients n=121 (59%)		Total n=205 (%)	p
		Microcytic n=53 (25.9%)	Normocytic n=62 (30.2%)	Macrocytic n=6 (2.9%)		
Sex						0.343
Female	35 (17)	17 (8.3)	30 (14.6)	3 (1.5)	85 (41.5)	
Male	49 (24)	36 (17.6)	32 (15.6)	3 (1.5)	120 (58.5)	
Age groups						<0.001
1-6	10 (4.9)	11 (5.4)	18 (8.8)	-	39 (19.0)	
7-24	9 (4.4)	21 (10.2)	6 (2.9)	1 (0.5)	37 (18.0)	
25-72	19 (9.2)	9 (4.4)	11 (5.4)	1 (0.5)	40 (19.5)	
73-144	22 (10.7)	11(5.4)	12 (5.8)	1 (0.5)	46 (22.5)	
145-216	24 (11.8)	1 (0.5)	15 (7.3)	3 (1.5)	43 (21.0)	
Admission reason						0.047
Acute infections	27 (13.2)	18 (8.8)	23 (11.0)	1 (0.5)	69 (33.6)	
HOD**	14 (6.8)	7 (3.4)	10 (4.9)	2 (1.0)	33 (16.1)	
Chronic disease	13 (6.4)	8 (3.9)	11 (5.4)	-	32 (15.6)	
Bleeding/trauma	5 (2.5)	3 (1.5)	9 (4.4)	1 (0.5)	18 (8.8)	
Epilepsy, MMR**	4 (1.9)	3 (1.5)	5 (2.5)	1 (0.5)	13 (6.4)	
Metabolic disease	14 (6.8)	8 (3.9)	2 (1.0)	1 (0.5)	25 (12.2)	
Postop, postarest	7 (3.4)	6 (2.9)	2 (1.0)	-	15 (7.3)	

n*: Number, HOD**: Hematooncologic disease, MMR***: Mental motor retardation

Table 2. RDW levels of patients according to anemia situation, admission reason, age groups and CRP

	Normal RDW n*=71 (34.6%)	Elevated RDW n=134 (65.4%)	Total n=205 (100%)	p
Anemia				**<0.001**
Non-enemic	46 (22.5)	38 (18.5)	84 (41.0)	
Mikrocytic anemia	4 (1.9)	49 (24.0)	53 (25.9)	
Normocyticanemia	19 (9.2)	43 (21.0)	62 (30.2)	
Macrocytic anemia	2 (1.0)	4 (1.9)	6 (2.9)	
Admission reason				0.142
Acute infections	23 (11)	46 (22.5)	69 (33.6)	
HOD**	11 (5.4)	22 (10.7)	33 (16.1)	
Chronic disease	6 (2.9)	26 (12.7)	32 (15.6)	
Bleeding/trauma	9 (4.4)	9 (4.4)	18 (8.8)	
Epilepsy, MMR***	5 (2.5)	8 (3.9)	13 (6.4)	
Metabolic disease	11 (5.4)	14 (6.8)	25 (12.2)	
Postop, postarest	6 (2.9)	9 (4.4)	15 (7.3)	
Age groups				0.008
0-6	8 (3.9)	31 (15.1)	39 (19.0)	
7-24	7 (3.4)	30 (14.6)	37 (18.0)	
25-72	15 (7.3)	25 (12.2)	40 (19.5)	
73-144	19 (9.2)	27 (13.3)	46 (22.5)	
145-216	22 (10.7)	21 (10.2)	43 (21.0)	
CRP			101 (49.2)	0.001
Normal	46 (22.5)	55 (26.7)		
Elevated	25 (12.1)	79 (38.7)	104 (50.8)	

n*: Number, HOD**: Hematooncologic disease, MMR***: Mental motor retardation, CRP: C-reactive protein, RDW: Red cell distribution width

elevation accompanied normocytic anemia. In children with low MCV and high RDW, iron deficiency is the first condition to be considered. When the cut-off value for RDW is accepted as 16.7% and for MCV as 72 FL, it has been shown that evaluating RDW and MCV together provides 70% sensitivity and 82.95% specificity for the diagnosis of iron deficiency (17). However, in critically ill children, these parameters vary due to infection and inflammation. For example, in iron deficiency anemia, ferritin is typically low, but during infection, ferritin may increase as an acute phase reactant in 25% of patients, masking iron deficiency (14,18). RDW indicates the extent to which the volume of each erythrocyte deviates from the mean erythrocyte volume. Although it has long been used as a parameter to determine the etiology of anemia, recent studies have suggested that RDW and the HGB/RDW ratio are useful in predicting mortality in critically ill patients and determining prognosis in cancer patients (19,20). Among patients with normal RDW levels, 22.5% had normal CRP levels, while 38.7% of patients with elevated RDW had elevated CRP levels. RDW was found to be elevated in normocytic anemias, in the age groups where normocytic anemia was common, and in diseases frequently admitted to intensive care. These results support that RDW may serve as an indicator of inflammation in critically ill children. Comprehensive large-scale studies are needed on this subject.

Study Limitation

Anemia was chosen as the study topic because it is frequently encountered in general pediatric practice. However, since the researchers' familiarity with the subject was limited, and their attention and perception were intended to focus more on the research process rather than the subject itself, the aim of the study was restricted to investigating the causes and frequency of anemia, while clinical course and mortality were not included. No additional tests or blood samples were taken for the purpose of this study. The results obtained during hospitalization were recorded. Therefore, etiological investigations, iron parameters, ferritin, and nutritional indicators remained incomplete. Since anemia is a multifactorial condition, it would be appropriate to plan comprehensive prospective studies in the future.

CONCLUSION

Anemia is a clinical finding that requires specific evaluation according to the patient's age and health status. Due to the low tolerance capacity for anemia in critically ill children and the negative impact of anemia on mortality and morbidity, complete blood count parameters of patients should be regularly monitored at the time of PICU admission and thereafter. The underlying cause of anemia should be identified, and it should be treated appropriately in accordance with clinical guidelines. Comprehensive studies with wide participation should be planned to determine the role of parameters such as ferritin and RDW, which serve as practical indicators in daily medical practice, in identifying the causes of anemia in critically ill patients.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee (decision no: 2938, date: 09.11.2023).

Informed Consent: Families of the patients included in the study were informed about the study and informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.İ., İ.A., Concept: K.İ., İ.A., M.B., M.Ba., M.Bo., M.Ç.K., M.Ö., Design: İ.A., M.Ba., M.Bo., M.Ç.K., M.Ö., Data Collection or Processing: K.İ., İ.A.,M.B., M.Ba., M.Bo., M.Ç.K., M.Ö., Analysis or Interpretation: K.İ., İ.A., M.B., M.Ba., M.Ç.K., M.Ö., Literature Search: İ.A., M.Bo., M.Ç.K., M.Ö., Writing: K.İ., İ.A., M.B., M.Ba., M.Bo.,M.Ç.K., M.Ö.

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Original Article

Are There Clinical and Laboratory Differences in COVID-19 Infection in Infants and Older Children? Single Center Experience

İnfantlarda ve Daha Büyük Çocuklarda COVID-19 Enfeksiyonunda Klinik ve Laboratuvar Olarak Farklılıklar Var Mıdır? Tek Merkez Deneyimi

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ABSTRACT

Objective: The clinic of coronavirus disease-2019 (COVID-19) infection can vary from asymptomatic to multi-organ failure. COVID-19 infections in infants have a different clinical course than adults and older children. In this study, it was aimed to evaluate the clinical course and laboratory findings of COVID-19 patients. It is also aimed to evaluate whether there is a different clinical or laboratory course of the disease in younger infants.

Material and Methods: In this study, 143 COVID-19 positive 1-216 months aged patients hospitalized and treated between 01.08.2021-30.04.2022 were included. Patients with chronic disease were not included in the study. SPSS version 24 was used for data analysis of the patients in our study. Those with p value of <0.05 were considered significant.

Results: Patients under 1 year of age were defined as Group 1, and those over 1 year of age were defined as Group 2. Of 73 patients in Group 1, 51 (80.8%) were male, 22 (19.2%) were female, of 70 patients in Group 2 45 (56%) were male, 35 (43%) were female (p<0.05). The mean age in Group 1 was 4.3 months (1-10), and in Group 2 it was 130 months (17-215). The most common complaints in Group 1 were fever (44%), cough (34%), and vomiting (13%). In Group 2, the most common complaints were fever (44%), cough (43%), and shortness of breath (27%). The length of stay was 6.1 days (2-15) in Group 1 and 8.3 days (3-24) in Group 2. This difference was statistically significant (p<0.05). Neutropenia was detected in 71.6% of the patients in Group 1 and in 20.5% of the patients in Group 2. The difference between lymphocyte and neutrophil counts between the two groups was statistically significant (p<0.05).

Conclusion: COVID-19 infection in children under one year of age shows differences both clinically and laboratory. In patients under one year of age, COVID-19 infection causes more neutropenia than lymphopenia.

Keywords: COVID-19, infant, lymphopenia, neutropenia

ÖZ

Giriş: Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu kliniği asemptomatikten, çoklu organ yetmezliğine kadar değişkenlik gösterebilmektedir. İnfantlardaki COVID-19 enfeksiyonları erişkin ve büyük çocuklardan farklı bir klinik gidişata sahiptir. Bu çalışmada COVID-19 hastalarının klinik seyri ve laboratuvar bulgularının değerlendirilmesi amaçlanmıştır. Ayrıca daha küçük infantlarda hastalığın farklı bir klinik veya laboratuvar seyri olup olmadığının değerlendirilmesi de hedeflenmiştir.

Gereç ve Yöntemler: Bu çalışmaya 01.08.2021-30.04.2022 tarihleri arasında yatırılarak tedavi edilen 143 COVID-19 pozitif çocuk hastası dahil edildi. 1-216 ay aralığındaki bu hastaların laboratuvar ve klinik verileri retrospektif olarak incelenmiştir. Kronik hastalığı olan hastalar çalışmaya dahil edilmedi. Çalışmamızdaki hastaların verileri analizi için SPSS versiyon 24 kullanıldı. P değeri <0,05 olanlar anlamlı kabul edildi.

Bulgular: Bir yaş altı hastalar Grup 1, 1 yaş üzeri ise Grup 2 olarak tanımlandı. Grup 1'deki 73 hastanın 51'i (%80,8) erkek, 22'ü (%19,2) kız, Grup 2'deki 70 hastanın 45'i (%56) erkek, 35'i (%43) kadındı (p<0,05). Grup 1 ortalama yaşı 4,3 ay (1-10), Grup 2'de 130 ay (17-215). Grup 1'de en sık şikayetler ateş (%44), öksürük (%34), kusma (%13) idi. Grup 2 de ise en sık şikayetlerin ateş (%44), öksürük (%43), nefes darlığı (%27)

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ÖZ

olduğu görüldü. Yatış süreleri Grup 1'de 6,1 gün (2-15), Grup 2'de 8,3 gün (3-24) olarak bulundu. Bu farklılık istatistiksel olarak anlamlıydı (p<0,05). Grup 1'deki hastaların %71,6'sında, Grup 2'deki hastaların %20,5'inde nötropeni tespit edildi. Her iki grup arası lenfosit ve nötrofil sayıları arası fark istatistiksel olarak anlamlı saptandı (p<0,05).

Sonuç: Bir yaş altındaki çocuklarda COVID-19 enfeksiyonu hem klinik hem de laboratuvar olarak farklılıklar göstermektedir. Bir yaş altı hastalarda COVID-19 enfeksiyonu bilinenin aksine lenfopeniden ziyade daha fazla nötropeniye sebep olmaktadır.

Anahtar Kelimeler: COVID-19, infant, lenfopeni, nötropeni

INTRODUCTION

In late 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, which caused pneumonia and respiratory failure cases in Wuhan-China, spread worldwide in a short time (1). While information on the course of coronavirus disease-2019 (COVID-19) in children was insufficient due to the low number of pediatric patients infected with SARS-CoV-2 at the beginning of the pandemic, clearer data on children were revealed later in the pandemic (2). In a review of 16266 research results and 63 publications, it was reported that the mortality risk in children was below 1%. The most common symptoms are fever (58%) and cough (50%). The rate of asymptomatic infection was found to be high (65%) (3).

COVID-19 infection causes complaints in a wide spectrum from mild upper respiratory tract infections to severe respiratory failure in older patients. In a study evaluating COVID-19 infections in newborn infants, it was reported that patients presented with fever, runny nose, vomiting and malnutrition (4). It was observed that pulmonary findings (pneumonia, bronchiolitis, cough…) were more prominent in older children, similar to adult patients. There are publications associating the presence of lymphopenia with critical severe disease in COVID-19 infection (5). When we look at the pathogenesis of the disease, a process that continues with excessive release of inflammatory cytokines is observed (6). These cytokines both cause clinical findings and lead to changes in laboratory findings. In the literature, although lymphopenia is more prominent in patients, neutropenia and thrombocytopenia have also been reported less frequently (7). In COVID-19, mechanisms such as increased lympholysis with viral invasion, increased lympholysis due to cytokine storm caused by the release of various cytokines, and increased lymphocyte destruction with metabolic disorders such as lactic acidosis are held responsible for lymphopenia (8).

Although lymphopenia similar to adults was observed in pediatric patients in the adolescent age group that we followed with COVID-19 infection in our clinic, we observed that neutropenia was more common than lymphopenia, especially in COVID-19 patients under one year of age. Based on this observation, we aimed to evaluate whether children under 1 year of age hospitalized with COVID-19 infection show different clinical and laboratory course.

MATERIALS and METHODS

Demographic, laboratory and clinical findings of 143 pediatric patients aged between 1 month and 18 years who were hospitalized with the diagnosis of COVID-19 between 01.08.2021-30.04.2022 in the Pediatric Infection Clinic of University of Health Sciences Türkiye, Adana City Training and Research Hospital were evaluated retrospectively. The patients were grouped as 73 infants under 1 year of age Group 1 and 70 patients over 1 year of age Group 2. While calculating the laboratory data of the patients, patients whose laboratory findings could be affected due to previous comorbidities (hematologic malignancy, congenital adrenal hyperplasia, sepsis, etc.) were excluded from the study.

Blood tests obtained at admission and 48 hours after hospitalization were evaluated. SPSS 24 was used for statistical data. Independent sample t-test was used for parametric calculations and comparisons between groups. Mean values ± standard deviations were given for laboratory findings. P value 0.05 was considered significant. Ethics committee approval for this study was obtained from University of Health Sciences Türkiye, Adana City Training and Research Hospital, Clinical Research Ethics Committee (decision number: 1962, date: 30.05.2022).

Findings

All patients were hospitalized in the ward and followed up. Of the 73 patients in Group 1, 51 (80.8%) were boys and 22 (19.2%) were girls, and of the 70 patients in Group 2, 45 (56%) were boys and 35 (43%) were girls (p<0.05). The mean age was 4.3 months (1-10) in Group 1 and 130 months (17-215) in Group 2. Intensive care unit was needed in 5 patients (5.5%) in Group 1 and 11 patients (15.7%) in Group 2 (p<0.05). The length of hospitalization was 6.1 days (2-15) in Group 1 and 8.3 days (3-24) in Group 2 (p<0.05). There was a statistically significant difference between the groups in terms of the need for intensive care and length of hospitalization (p<0.05). When clinical findings were compared between the groups, the most common complaints in Group 1 were fever (44%), cough (34%), and vomiting (13%), while the most common complaints in Group 2 were fever (44%), cough (43%), and dyspnea (27%). In Group 1, diarrhea was more common in Group 1 compared to other findings (p<0.05). In Group 2, vomiting, tachypnea and pulmonary findings (pneumonia, bronchiolitis, cough) were more frequent and statistically

significant (p<0.05). Demographic and clinical findings of the patients included in the study are given in Table 1.

When the examinations of the patients at the time of admission were analyzed, the total white blood cell count of the patients in Group 1 was 9874/mm^3 and the total white blood cell count of the patients in Group 2 was 7186/mm^3 (p>0.05); the lymphocyte count of the patients in Group 1 was 4877/mm^3 and the lymphocyte count in Group 2 was 2009/mm^3 (p<0.05); neutrophil count was 3493/mm^3 in Group 1 patients and 4335/mm^3 in Group 2 patients (p>0.05); platelet count was 369412.70/mm^3 in Group 1 patients and 242603.77/mm^3 in Group 2 patients (p>0.05). C-reaktif protein was 7.4 mg/L in Group 1 and 35.2 mg/L in Group 2 (p<0.05). Procalcitonin was 0.1887 mg/L in Group 1 patients, while procalcitonin was 0.6829 mg/L in Group 2 patients (p<0.05).

The total white blood cell count of the patients in Group 1 was 7861/mm^3, while the total white blood cell count of the patients in Group 2 was 5815/mm^3 (p>0.05); the lymphocyte count of the patients in Group 1 was 5107/mm^3, while the lymphocyte count of the patients in Group 2 was 2125/mm^3 (p<0.05); neutrophil count was 1468/mm^3 in Group 1 and 2757/mm^3 in Group 2 (p<0.05); platelet count was 372158/mm^3 in Group 1 and 232673/mm^3 in Group 2 (p<0.05). No significant difference was observed in other laboratory tests of the patients. Detailed data regarding the laboratory findings of the patients are given in Table 2. Table 3 shows the rates of lymphopenia and neutropenia according to age in the patients included in the study. While the frequency of neutropenia was higher in children between the ages of 1-12 months, the frequency of lymphopenia increased in older children.

DISCUSSION

In this study, we evaluated the data of patients diagnosed with COVID-19 in pediatric patients in a 9-month period as the largest and most comprehensive COVID-19 patient treatment and follow-up center in the south and southeast. The patients included in our study had clinical presentation and disease symptoms that varied between age groups. In the literature, it has been reported that COVID-19 infection usually proceeds with non-specific findings in children. However, there are publications reporting that a small number of patients with symptoms presented with upper respiratory tract infection findings, mostly lower respiratory tract infection (2).

In a previously published article, it was reported that children younger than 1 year of age represented 0.27% of all patients of all ages in the USA. In addition, this rate is even lower for newborns and infants (9).

In addition, the clinical presentation of pediatric COVID-19, the disease caused by SARS-CoV-2, differs significantly from that of the elderly. As previously published articles emphasize, infants and children often have mild symptoms and very low mortality rates (10,11).

In our literature review, in a previously published retrospective study, similar to our study, it was reported that COVID-19 infection in children most commonly caused fever and cough symptoms and progressed with mild to moderate clinical findings (12). In another comprehensive article comparing children and adolescents, similar to our study, it was reported that COVID-19 infection caused a milder clinical course in young children (13). In another study by Maltezou et al. (14) it was reported that cough and fever were the most common symptoms during COVID-19 infection in children, while other symptoms included diarrhea, vomiting and dyspnea, although to a lesser extent. The findings of Maltazeu et al. (14) also support this study we have completed.

Patients in Group 1 had milder symptoms such as fever, malnutrition and vomiting and a shorter hospitalization period (6.1 days). On the other hand, patients in Group 2 had a clinically longer need for hospitalization (8.3 days). There was a statistically significant difference between the groups in length of hospitalization (p<0.005).

In our literature review, in a previously published retrospective study, similar to our study, it was reported that COVID-19 infection in children most commonly caused fever and cough symptoms and progressed with mild to moderate clinical findings (12). In another comprehensive article comparing

Table 1. Demographic and clinical findings of the patients included in the study

	Group 1	Group 2	p
	Number of patients (n) and percentage (%)		
Gender Female Male	 22 (19.2%) 51 (80.8%)	 29 (41.4%) 41 (58.6%)	0.009
Fever	44 (60.3%)	44 (62.9%)	0.53
Cough	34 (46.6%)	43 (61.4%)	0.086
Diarrhea	12 (16.4%)	7 (10%)	0.023
Vomiting	13 (17.8%)	26 (37.1%)	0.001
Tachypnea	6 (8.2%)	27 (38.6%)	0.001
Lung findings	14 (19.2%)	46 (65.7%)	0.001
Length of stay (days)	6.1	8.3	0.003

Table 2. Laboratory findings of the patients included in the study

Parameters	Group 1	Group 2	p
White blood cell count (mm^3) on admission White blood cell count (mm^3) after 48 hours	9874.60±3676.86 7861.90±2618.01	7186.79±4026.54 5815.38±3616.54	0.901 0.316
Neutrophil (mm^3) on admission Neutrophil (mm^3) after 48 hours	3493.65±2462.81 1468.27±756.44	4335.85±2270.89 2757.69±1679.20	0.805 **0.001**
Lymphocyte (mm^3) on admission Lymphocyte (mm^3) after 48 hours	4877.78±2341.31 5107.94±2384.37	2009.43±2108.97 2125.00±2184.78	0.081 0.160
Platelet (mm^3) on admission Platelet mm^3) after 48 hours	369412.70±114381.03 372158.73±129023.15	242603.77±87941.92 232673.08±94015.37	0.265 **0.009**
Ddimer (ng/L) at admission Ddimer (ng/L) after 48 hours	1127.16±1083.22 2087.05±4853.32	869.75±652.92 1202.56±1191.87	0.305 **0.007**
Fibrinogen (mg/L) at admission Fibrinogen (mg/L) after 48 hours	210.18±76.18 198.96±75.51	300.40±100.71 263.60±72.73	0.247 0.822
Troponin (ng/L) at admission Troponin (ng/L) after 48 hours	28.86±98.23 24.44±73.94	3.33±2.87 2.50±1.04	0.722 0.623
Ferritin (µg/L) at admission Ferritin (µg/L) after 48 hours	210.64±322.58 198.56±286.58	156.58±234.69 223.98±464.11	0.973 **0.021**
CRP (mg/L)	7.46±12.89	35.20±48.08	**0.001**
Procalsitonin (mg/L)	0.18±0.17	0.68±0.98	**0.001**
AST (U/L)	54.07±43.12	42.46±17.74	0.919
ALT (U/L)	33.79±23.67	36.00±30.60	**0.036**
LDH (U/L)	374.58±127.75	327.67±132.33	0.064

CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

Table 3. Neutropenia and lymphopenia of the patients included in the study according to age

Parameters	Group 1 (1 month-12 months) n (%)	Group 2 (12 months-216 months) n (%)	p
Neutropenia according to age at admission Neutropenia after 48 hours according to age	35 (48%) 52 (71.6%)	6 (8.8%) 14 (20.5%)	**0.002** **0.000**
Lymphopenia at admission according to age Lymphopenia after 48 hours according to age	23 (31.3%) 25 (34.3%)	42 (60.2%) 42 (60.2%)	**0.001** 0.002

children and adolescents, similar to our study, it was reported that COVID-19 infection caused a milder clinical course in young children (13). In another study by Maltezeu et al. (14) it was reported that cough and fever were the most common symptoms during COVID-19 infection in children, while other symptoms included diarrhea, vomiting and dyspnea, although to a lesser extent. The findings of Maltazeu et al. (14) also support this study we have completed.

In the patients we followed up in our clinic, pneumonia was the most common reason for hospitalization in patients over 1 year of age, while patients under 1 year of age required hospitalization due to clinically resistant fever, malnutrition and bronchiolitis. Severe clinical picture and significant lung involvement were not observed in these patients in Group 1. Yang et al. (5) reported the presence of lymphopenia in critically severe COVID-19 infection in adult patients. Similar to this article, our patients in Group 2 also had lymphopenia in addition to pneumonia. ACE-2 receptors are present on the surface of lymphocytes (15). SARS-CoV-2 can infect lymphocytes directly through this receptor and may also cause a viral pneumonia since it is also present on the lung surface (16). In our patients over 1 year of age, lymphopenia and pneumonia were observed similar to adult patients, whereas we did not find pneumonia and marked lymphopenia in infants. The fact that there was more lymphopenia and pneumonia in Group 2 supports that ACE-2 receptors are expressed more in older children than in infants.

In addition to the differences in clinical findings, there were also significant differences in laboratory parameters between the patient groups. While neutropenia was more prominent in Group 1, lymphopenia was more prominent in Group 2. While lymphopenia occurred in 20% of Group 1, 60% of patients in Group 2 had lymphopenia. The difference in the predominance of neutropenia or lymphopenia according to age between the groups suggests that this may be the reason for the difference in clinical findings.

There are many opinions on how lymphopenia occurs in COVID-19 (8). Causes such as lympholysis caused by

viral invasion of lymphocytes due to the ACE-2 gene on lymphocytes, disruption of lymphocyte production and destruction balance by cytokine storm causing lymphoid organ atrophy, inhibition of lymphocyte proliferation in the presence of lactic acidosis cause lymphopenia (8). The main cytokines causing cytokine storm are interleukin (IL)-6, IL-2, IL-7. Granulocyte colony-stimulating factor, IFN-8, MCP-1, MIP1-α and TNF-α also cause lymphocyte apoptosis and lymphopenia (8). In patients under 1 year of age, since these immune mechanisms are still immature, lymphopenia does not occur, suggesting that neutropenia occurs with a different immune pathway.

Similar to the predominance of neutropenia found in Group 1, neutropenia but not lymphopenia was reported in a study evaluating infants and newborns under 3 months of age (4).

It is known that neutropenia occurs in viral infections including varicella, measles, rubella, hepatitis A and B, influenza, cytomegalovirus, ebstein-barr virus, parvovirus B19, adenovirus and coxsackie in childhood due to decreased production and increased destruction (17). COVID-19 acts similarly to these viral agents, suggesting that it causes neutropenia in children under the age of 1 year.

CONCLUSION

Compared to other age groups, infants had milder clinical course during the course of COVID-19 infection and laboratory findings showed neutropenia, although no significant lymphopenia was observed. In patients under 1 year of age presenting with fever and neutropenia, COVID-19 infection should be considered in the differential diagnosis. The fact that lymphopenia becomes more pronounced as the age of the patient increases suggests that different immune pathways are affected. The affected patient groups and clinical effects also change with variant changes. Although the COVID-19 epidemic period is over, it will continue its seasonal activity in the following years. Therefore, infants should also be evaluated for COVID-19 infection in the presence of neutropenia.

Ethics

Ethics Committee Approval: Ethics committee approval for this study was obtained from University of Health Sciences Türkiye, Adana City Training and Research Hospital, Clinical Research Ethics Committee (decision number: 1962, date: 30.05.2022).

Informed Consent: This study is a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.K.G., E.A.T., A.H.T., M.D.E., M.K.Ç., Ü.Ç., Concept: Ü.Ç., Design: T.K.G., Ü.Ç., Data Collection or Processing: T.K.G., E.A.T., A.H.T., Analysis or Interpretation: T.K.G., Literature Search: M.D.E., M.K.Ç., Writing: T.K.G., Ü.Ç.

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Case Report

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Zuclopenthixol-related Perioral Dermatitis: Treatment Challenges in the Triad of Autism Spectrum Disorder, Attention Deficit/Hyperactivity Disorder, and Conduct Disorder

Zuklopentiksol Kullanımı Sonrası Perioral Dermatit: Otizm Spektrum Bozukluğu, Dikkat Eksikliği/Hiperaktivite Bozukluğu ve Davranım Bozukluğu Üçgeninde Tedavi Zorlukları

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ABSTRACT

A 12-year-old boy with autism spectrum disorder, attention deficit/hyperactivity disorder, and conduct disorder developed perioral rash after zuclopenthixol injection in addition to olanzapine and guanfacine treatment. The onset of rash within 48 hours after the injection may suggest a clear relationship in terms of timing. Also, the Naranjo score of 6 may support that zuclopenthixol is the probable reason for this adverse reaction. The rapid regression after discontinuation of the drug may further reinforce the specificity of this relation.

Keywords: Zuclopenthixol, perioral dermatitis, antipsychotic side effects, autism spectrum disorder, adverse drug reaction, pharmacovigilance

ÖZ

Bu olgu sunumunda otizm spektrum bozukluğu, dikkat eksikliği/hiperaktivite bozukluğu ve davranım bozukluğu tanılarıyla takip edilen 12 yaşındaki erkek hastada olanzapin ve guanfasin tedavisine ek olarak uygulanan zuklopentiksol dekanoat enjeksiyonu sonrası gelişen perioral dermatit olgusu ele alınmaktadır. Enjeksiyondan sonraki 48 saat içinde döküntülerin başlaması, zamanlama açısından belirgin bir ilişkiyi düşündürmektedir. Ayrıca, uygulanan Naranjo skorunun 6 olması, zuklopentiksolün bu reaksiyona neden olma olasılığını güçlü bir şekilde desteklemektedir. İlacın kesilmesiyle döküntünün hızla gerilemesi ise bu ilişkinin spesifikliğini daha da pekiştirmektedir.

Anahtar Kelimeler: Zuklopentiksol, perioral dermatit, antipsikotik yan etkileri, otizm spektrum bozukluğu, advers ilaç reaksiyonu, farmakovijilans

INTRODUCTION

Autism spectrum disorder (ASD) is a complex, lifelong neurodevelopmental disorder characterized by persistent deficits in social communication and repetitive behavioral patterns (1). Current epidemiological data report that one in every 31 children has ASD (2). ASD frequently coexists with various psychiatric conditions, such as attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD), intellectual disability, and anxiety disorders (3).

Although the basic treatment approach for ASD is individualized special education, pharmacotherapy is frequently employed in the presence of comorbid disorders, especially ADHD and CD. In clinical practice, methylphenidate, atomoxetine, and guanfacine are commonly used to manage ADHD symptoms. For comorbid CD or pronounced behavioral dysregulation, second-generation and typical antipsychotics, including risperidone, aripiprazole, olanzapine, and haloperidol, may be introduced. Combined pharmacotherapy may also be considered in complex cases (4-6).

Olanzapine is an atypical antipsychotic that exerts antagonistic effects on dopamine (D2) and serotonin (5HT2A, 5HT2C) receptors (5). It has demonstrated clinical efficacy in managing symptoms associated with

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non-schizophrenic psychotic disorders, impulse control disorders, CD, and ASD.

Guanfacine acts by stimulating presynaptic alpha-2 adrenergic receptors in the central nervous system (6). This effect contributes to the relief of behavioral symptoms such as hyperactivity and aggression by increasing attention and impulse control and can be used alone or in combination treatments (4-6).

Zuclopenthixol is a typical antipsychotic with high affinity for dopamine D1 and D2 receptors. Although it carries the risk of extrapyramidal side effects like other typical antipsychotics, it can be preferred in some cases due to its long-acting decanoate formulation. The intramuscular decanoate formulation reaches peak plasma concentrations within 3 to 7 days and has an elimination half-life of approximately 19 days. It is commonly utilized in the management of severe aggression, particularly in individuals with CD (7).

In this paper, we present a rare adverse event that has not been previously reported in the current literature: a perioral dermatitis, which developed after the administration of zuclopenthixol decanoate on ongoing olanzapine and guanfacine treatment.

CASE REPORT

The focus of this presentation is a 12-year-old boy who was followed up in our outpatient clinic with the diagnoses of ASD, ADHD, and CD. The patient's anamnesis indicated that despite receiving risperidone and atomoxetine treatment for seven years, his behavioral problems and hyperactivity continued. He tended toward aggressive behaviors directed at family members, special education staff, and peers. The childhood autism rating scale score was 51, and the problem behavior checklist score was 107. Guanfacine and olanzapine treatments were gradually started. The patient used guanfacine 3 mg/day and olanzapine 10 mg/day for the last two months and had no side effects. However, the treatment dose was increased to guanfacine 4 mg/day and olanzapine 15 mg/day due to the continuation of behaviors like not obeying the rules at school, being constantly on the move, and harming everything and everyone around him. Since the dose increment was not very beneficial, an intramuscular injection of 200 mg zuclopenthixol decanoate was applied in addition to the current treatment.

Forty-eight hours after the injection, the patient came to our clinic with rashes around the mouth (Figure 1. A). Physical examination revealed elevated, crusted, and painless skin lesions localized around the mouth. The child did not have habits such as putting foreign objects in the mouth or touching/licking the oral area. There was no previous history of a similar lesion, and no similar condition was observed in any other family members that would suggest a contagious infection. Additionally, there was no use of a different medication and no change in the patient's diet or daily life routine.

The patient was referred to the pediatrics and dermatology departments for detailed examination and evaluation. The dermatology clinic diagnosed the rashes as perioral dermatitis, with no evidence of infectious or systemic etiology, suggesting a possible drug-related reaction (Figure 1. B). In laboratory tests, hemogram and biochemical parameters were found to be within normal limits. Local cortisone treatment was started for the lesions.

The patient continued to use guanfacine 4 mg/day and olanzapine 15 mg/day since he benefited from these doses during the regression of perioral dermatitis. The local cortisone treatment was applied for two weeks, and the lesions around the mouth completely resolved (Figure 1. C). Due to complaints of insomnia and agitation reported during clinical interviews, the olanzapine dosage was increased to 20 mg/day, and perioral dermatitis did not recur during the follow-up.

DISCUSSION

Antipsychotic medications can lead to various adverse cutaneous reactions. These reactions may range a wide spectrum from benign lesions, such as eczema, erythema, pigmentation, photosensitivity, urticaria, and pruritus, to serious conditions like life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis (8). Possible mechanisms of these dermatological reactions include immunomodulation, accumulation of toxic metabolites, and photosensitization (8). Also, the increase in prolactin levels may stimulate sebum production and exacerbate cutaneous reactions (9,10). On the other hand, thioxanthene-based antipsychotics, especially zuclopenthixol, have the potential to predispose to phototoxic reactions (11).

In the present case, erythematous, scaly lesions were observed in the perioral region, and the lesions were accompanied by subjective symptoms such as itching. Although the pathogenesis of this reaction has not been fully elucidated, the immunomodulatory effects of antipsychotics may play an important role. Antipsychotics can trigger inflammatory

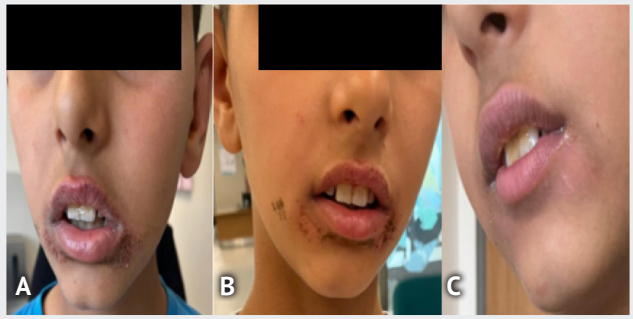

Figure 1. The occurrence and regression of perioral dermatitis after zuclopenthixol decanoate injection in a 12-year-old boy A) 2 days after the injection, B) 5 days after the injection, C) Lessions resolved in 2 weeks

Table 1. Naranjo adverse drug reaction scale

No.	Question	Response	Score
1.	Are there previous conclusive reports on this reaction?	Not known or not done	0
2.	Did adverse event appear after the suspected drug was given?	Yes	2
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes	1
4.	Did the adverse reaction appear when the drug was readministered?	Not known or not done	0
5.	Are there alternative causes that could have caused the reaction?	No	2
6.	Did the reaction reappear when a placebo was given?	Not known or not done	0
7.	Was the drug detected in any body fluid in toxic concentrations?	Not known or not done	0
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Not known or not done	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Not known or not done	0
10.	Was the adverse event confirmed by any objective evidence?	Yes	1
	Total score		**6**

Scoring: >9 = definite ADR; 5-8 = probable ADR; 1-4 = possible ADR; 0 = doubtful ADR
ADR: Adverse drug reactions

responses by changing the cytokine balance (12). Similar mechanisms have been described, particularly with beta-lactam antibiotics and some anticonvulsants, suggesting that non-drug-specific immune-mediated dermatological side effects may occur (13). Additionally, zuclopenthixol may contribute to the pathophysiological process by disrupting epidermal barrier function or increasing neurogenic inflammation through dopaminergic effects (14,15).

In our case, the dermatitis occurred only two days after the zuclopenthixol injection, suggesting a drug-induced hypersensitivity reaction. The naranjo scale was 6 for zuclopenthixol, supporting the probability of drug-relatedness (Table 1). The patient was using olanzapine and guanfacine simultaneously, and drug interactions might also trigger this dermatological side effect. The potent M3 muscarinic antagonism of olanzapine (5) may impair stratum corneum hydration in the perioral region by suppressing sweat and sebum production. This pharmacological effect may predispose to the development of perioral dermatitis, which is particularly prone to transepidermal water loss (16). Moreover, the weakening of the skin barrier may be further enhanced by guanfacine's reduction of local tissue perfusion via α2A adrenergic receptors (17).

In this case, perioral dermatitis completely regressed after zuclopenthixol was discontinued, and the findings did not recur despite the olanzapine dose being increased. This may show that the dermatitis was primarily due to zuclopenthixol. On the other hand, dermatitis associated with olanzapine has been reported in the literature (18); it is seen that olanzapine alone did not cause a similar side effect in this patient. There are examples that synergistic adverse effects can occur, especially in the combination of antipsychotics with other psychotropic drugs (19). This may support that the dermatitis in our case may be due to a possible synergistic effect between olanzapine and zuclopenthixol. The combination of D2 receptor blockade by zuclopenthixol and the anticholinergic properties of olanzapine may have triggered a localized skin inflammation (5,7). The metabolism of both drugs via the CYP2D6 enzyme system may also bring an interaction at the pharmacokinetic level to the agenda (7).

While olanzapine has been frequently associated with cutaneous adverse drug reactions, including serious manifestations such as DRESS syndrome (20), dermatological complications from zuclopenthixol are infrequently described.

CONCLUSION

We present a rare case of perioral dermatitis related to zuclopenthixol decanoate injection. In clinical practice, when similar dermatological findings are encountered, possible side effects related to antipsychotic drugs should be taken into consideration, and the treatment plan should be revised if necessary. It should be remembered that drug interactions may pose a risk in combination treatments. New case reports and comprehensive pharmacovigilance studies are needed for a better understanding and management of such reactions.

Ethics

Informed Consent: Written assent from the patient and consent from his parents/guardians were received for publication of this case report.

Footnotes

Author Contributions

Surgical and Medical Practices: E.G.Y.A., D.A.V., S.G., Concept: D.A.V., Design: D.A.V., S.G., Data Collection or Processing: E.G.Y.A., Analysis or Interpretation: S.G., Literature Search: E.G.Y.A., Writing: E.G.Y.A.

Conflict of Interest: All authors declare that they have no conflict of interest.

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