Respiratory symptoms of COVID-19 in an adolescent patient with WHIM syndrome: a clinical case

Abstract. In case of coronavirus disease 2019 (COVID-19) in children suffering from primary immunodeficiency, the last one can be an aggravating or a mitigating factor of the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome is usually classified as severe congenital neutropenia, but most patients have multiple leukocyte deficits, even panleukopenia, and therefore it can also be classified as severe combined immunodeficiency. B-lymphopenia is especially severe, and this probably partly explains the hypogammaglobulinemia. This rare disease, caused by autosomal dominant mutations, is a combined variant of immunodeficiency, which includes myelokathexis, susceptibility to infections, and hypogammaglobulinemia. Myelokathexis is a unique form of acyclic severe congenital neutropenia caused by the accumulation of mature and degenerative neutrophils in the bone marrow. Monocytopenia and lymphopenia, especially B-lymphopenia, also occur. In some patients, there are defects in the development of the cardiovascular, genitourinary and nervous systems, which in general can contribute to the extremely severe course of infectious inflammatory process, in particular due to the SARS-CoV-2. Objective: to analyze the clinical and laboratory peculiarities of coronavirus disease caused by SARS-CoV-2 in immunosuppressed patients on the example of a clinical case of COVID-19 in a child with previously diagnosed WHIM syndrome. Materials and methods. The article presents our own observation of coronavirus disease in a female adolescent suffering from previously verified primary immunodeficiency (WHIM syndrome) in the period after surgical routine correction of patent ductus arteriosus. On the 2nd day of sudden disease onset, the child was hospitalized in moderate condition with signs of airway inflammation as rhinopharyngitis and obstructive bronchitis. Results. Laboratory tests showed leukopenia, absolute neutropenia, increased levels of procalcitonin, C-reactive protein, D-dimer in serum and a reduction of activated partial thromboplastin time. The treatment included hydrobalance protection per os and by infusion, systemic and topical inhalation therapy with a short steroids course, antibacterial therapy as fourth generation cephalosporins, intravenous granulocyte colony stimulating factor, and symptomatic treatment. The girl’s condition became progressively better, she was discharged from the hospital on the 7th day to continue treatment at the outpatient setting. Conclusions. The severity of respiratory pathology and the prognosis of COVID-19 depend on the immunodeficiency type and compromised part of immune system, as well as the heterogeneity of new SARS-CoV-2 strains. The aggravating/protective role of primary immunodeficiency, in particular WHIM syndrome, in determining COVID-19 severity is currently limited because of small number of observations and requires further data collection. The presented clinical case describes the classic moderate coronavirus disease as airway infection in an adolescent suffering from primary immunodeficiency.

Keywords: children; coronavirus disease COVID-19; respiratory manifestations; WHIM syndrome
Introduction

The rapid spread of coronavirus disease 2019 (COVID-19) now offers more clues on how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) evolves in pediatric population and outlines risk factors that cause severe coronavirus disease. Early after the new severe SARS-CoV-2 was first described, there was a misconception circulating that children are less likely to get infected by the virus than adults. Now it became clear that children are equally capable of getting infected by SARS-CoV-2, however they are more likely to develop mild symptoms compared with primary infection occurring in adults [1].

COVID-19 can be asymptomatic or can cause a range of symptoms such as fever, dry cough, fatigue, and a runny or stuffy nose. Other complaints include gastrointestinal problems as well. Most children with a mild illness get better within 1–2 weeks from the day showing first symptoms. There are fewer cases when the virus affects the lower respiratory tract [2].

Although most pediatric patients with COVID-19 have milder symptoms and good prognosis compared to adults, children remain as vulnerable to the virus as adults. Despite better prognosis for pediatric patients with COVID-19 to get clean recovery, the number of children that develop serious complications such as multisystem inflammatory syndrome is rising [3]. There are cases when children develop life-threatening symptoms with one or more underlying pathologies [4, 5]. Comorbid conditions in children, including immunodeficiency, diabetes, asthma and chronic renal failure, had an increased risk of COVID-19-related severe morbidity and required hospitalization and lung ventilation support [6].

Risk factors for severe disease and mortality from COVID-19 include advancing age and comorbidities associated with direct or indirect suppression of the immune system. The consequences of SARS-CoV-2 infection in individuals with primary immunodeficiency (PID) remain uncertain [7]. In the absence of large and/or thorough data, it remains unclear whether PID is a predisposing or, paradoxically, a protective factor for SARS-CoV-2 infection [8]. SARS-CoV-2 infection in children with PID and its complications have not yet been well described, the course of COVID-19 can range from mild illness to death. A larger international retrospective study reported the clinical course of 94 patients with PID, primarily adults, with approximately 30% of patients having asymptomatic or mild infection, and major risk factors for disease severity including comorbidities also present in the general population [9].

Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is an extremely rare, combined primary immunodeficiency disorder found worldwide, with estimated incidence of 0.23 cases per million births. Almost all WHIM patients have myelokathexis and recurrent infections, and most but not all will eventually develop refractory warts. Hypogammaglobulinemia is the least penetrant phenotype. Myelokathexis refers to retention of neutrophils in the bone marrow. All but a few cases of WHIM syndrome are caused by autosomal dominant gain-of-function mutations in the G protein-coupled, cysteine-X-cysteine chemokine receptor type 4 (CXCR4) [10, 11]. Infections of the upper respiratory tracts and lesions due to human papillomavirus are common [12].

WHIM syndrome is usually classified as severe congenital neutropenia, but most patients have multiple leukocyte deficits [13, 14], even panleukopenia [15], and therefore it also be classified as severe combined immunodeficiency. B-lymphopenia is especially severe, and this probably partly explains the hypogammaglobulinemia [16]. This rare disease, caused by autosomal dominant mutations, is a combined variant of immunodeficiency, which includes myelokathexis, susceptibility to infections, and hypogammaglobulinemia. Myelokathexis is a unique form of acyclic severe congenital neutropenia caused by the accumulation of mature and degenerative neutrophils in the bone marrow. Monocytopenia and lymphopenia, especially B-lymphopenia, also occur [11].

Given the potential risk factors, children with immunodeficiency are at higher risk of severe COVID-19. In order to protect such children, the necessary precautions should be taken such as individually adjusted treatment strategy combined with various therapeutic approaches [17].

The clinical implications of SARS-CoV-2 infection in children with compromised immune system are highly variable and our data of patients with COVID-19 with primary immunodeficiency is insufficient. We report a case of COVID-19 infection with a rare primary immunodeficiency disorder, WHIM syndrome, in an adolescent patient.

Objective: to observe clinical and laboratory features of severe COVID-19 associated with underlying WHIM syndrome among children.

Materials and methods

In February 2022, in the Regional Municipal Non-Profit Facility “Chernivtsi Regional Children’s Clinical Hospital”, a 15-year-old girl has been undergoing inpatient treatment for acute bronchitis, 2019-nCoV acute respiratory infection. Previously, she was diagnosed with WHIM syndrome. The patient was examined and recommended treatment in accordance with applicable national standard guidelines and local protocols.

Results and discussion

We present a clinical case of coronavirus disease caused by SARS-CoV-2 in a female adolescent suffering from existing primary immunodeficiency — WHIM syndrome. A 15-year-old female patient presented to the emergency department with dry cough and dizziness followed by a history of fever (38.2°C), runny nose and total body weakness of 2 days.

Upon admission to the isolation ward of infectious diseases department of the Regional Municipal Non-Profit Facility “Chernivtsi Regional Children’s Clinical Hospital”, the patient had mild symptoms such as respiratory tract infection and intoxication syndrome. The girl’s me-
dical history records that the young patient is a second child that was delivered vaginally at 41 weeks, with weight of 3 kg, height of 50 cm, and was diagnosed with birth asphyxia and dacryocele within the first week of life.

In early childhood, the patient often suffered from respiratory tract infections, in particular, recurrent bilateral suppurative otitis media, community-acquired pneumonia, as well as vulvovaginal candidiasis and acute pylonephritis. In middle childhood, the girl was diagnosed with synovitis, recurrent chronic pylonephritis, 3 episodes of community-acquired pneumonia, chicken pox, measles and whooping cough.

When the patient was 12 years old, she had a diagnosis of WHIM syndrome on the basis of molecular genetic testing conducted by Invitae laboratory (USA) that detected mutations in the CXCR4 gene c.1000C>T (p.Arg334*), heterozygous pathogenic. Subsequently, according to the results of the myelogram, there was a decrease in the number of cellular elements in bone marrow preparations with preservation of granulocyte and megakaryocyte hematopoietic progenitors; hyposegmentation of segmented neutrophil nuclei was detected, the share of blast cells was 1.8 %.

Besides the routine immunization according to National Vaccination Calendar of Ukraine, the patient was additionally vaccinated against pneumococcus and meningococcal disease that is caused by the strains A, C, Y and W-135.

In January 2022, the girl underwent planned successful endovascular closure of patent ductus arteriosus performed in the Center of Pediatric Cardiology and Cardiac Surgery (Kyiv, Ukraine).

There have been a few confirmed cases of COVID-19 within the family circle one week prior to the surgery.

When examined, the patient was conscious, did not present confusion or difficulty speaking or understanding speech. Physical development is average, harmonious, mental development is not disturbed. The pupils are equal in size, D = S, round, symmetrical, responsive to light and convergence. There were no signs of facial nerve damage, facial expressions are good. Muscle tone of the upper extremities is good. Tendon reflexes (biceps, triceps, carporadial) are not normal. The skin is pale, clean. Eyes are moist, pharynx is inflamed. Skin turgor and skin elasticity are good. Respiratory rate is 22 per minute. Breath is coarse, wheezing lung sounds. Oxygen saturation level is 96 %. Heart sound is normal, heart rate is 98 beats per minute. Abdomen is soft, symmetric, and non-tender without distention. Body temperature is 37.4 °C.

Additional tests to determine the cause of respiratory tract infections included:

— rapid SARS-CoV-2 antigen test (nasopharyngeal swab) — positive;
— polymerase chain reaction (nasopharyngeal swab) — positive.

Based on the available data and patient’s medical history, we can conclude a diagnosis of 2019-nCoV acute respiratory disease, acute obstructive bronchitis, respiratory failure type 1–2, primary immunodeficiency disease (WHIM syndrome). Signs of COVID-19 examined in this review include acute respiratory infection, close contact with COVID-19 patients, inflamed pharynx, coarse breath and wheezing lung sounds, leucopenia and neutropenia, positive polymerase chain reaction (nasopharyngeal swab), chest X-ray picture (increased pulmonary vascularity, deformation of the roots), the results of previous genome sequencing.

For patients with primary immunodeficiency, the development of severe symptoms due to COVID-19 is of concern. Therefore, the treatment has to consider severity of COVID-19 as well as address the specific clinical symptoms of each individual affected by immune deficiency disorder. Therapy should include respiratory and hemodynamic support, anti-inflammatory and anti-thrombotic medications.

There is no standard management for COVID-19 patients with primary immunodeficiency and symptoms vary from one individual to another. Antibacterial treatment should be directed toward the symptoms that are apparent for each individual if any presented.

Our patient has been receiving intravenous fluid drips to maintain the balance of body fluids, systemic and topical short-term anti-inflammatory inhalation therapy along with symptomatic treatment.

With regards to WHIM syndrome, the girl has been receiving injections of granulocyte colony stimulating factor to help normalize hematological parameters. Since the patient was diagnosed with chronic pylonephritis and recently underwent surgical procedure, she was prescribed first-line empiric therapy with fourth generation cephalosporins to prevent co-infections. The patient responded well to the treatment and was discharged from the hospital after 7 days to continue outpatient treatment.

Conclusions

1. The presented article describes a clinical case of COVID-19 in a female adolescent patient with a primary immunodeficiency. The girl developed mild symptoms that targeted upper and lower respiratory tract.
2. The severity of the infection and recovery prognosis depend on the nature of immunodeficiency disorder and differs between SARS-CoV-2 strains.
3. A treatment plan for a patient with mild COVID-19 infection that presented with bronchitis and preexisting WHIM syndrome included dehydration, systemic and topical anti-inflammatory therapy. As for antibacterial treatment, it is advisable for doctors, who manage patients with WHIM syndrome, to choose a directed treatment that is apparent for each individual. It may require the coordinated efforts of different specialists and may need to adjust treatment plan in the future.

4. Our understanding of COVID-19 illness with overlapping WHIM syndrome is quite limited at the moment. Further sufficient epidemiologic data collection is required.

The authors declare that this article is original, has not been published before and is not currently being considered for publication elsewhere.

References


Information about authors

R.V. Tkachuk, PhD student at the Department of Pediatrics and Pediatric Infectious Diseases, Bukovinian State Medical University. e-mail: tkachuk.roman@bsmu.edu.ua; https://orcid.org/0000-0002-6575-2365

O.K. Koloskova, MD, PhD, Professor, Head of the Department of Pediatrics and Pediatric Infectious Diseases, Bukovinian State Medical University. e-mail: koloskova.olegna@bsmu.edu.ua; https://orcid.org/0000-0002-4462-8756

M.N. Garas, PhD, MD, Associate Professor, Department of Pediatrics and Pediatric Infectious Diseases, Bukovinian State Medical University. e-mail: garas.mykola@bsmu.edu.ua; https://orcid.org/0000-0001-7304-2090

T.M. Blouos, PhD, MD, Associate Professor, Department of Pediatrics and Pediatric Infectious Diseases, Bukovinian State Medical University. e-mail: blouos.tetiana@bsmu.edu.ua; https://orcid.org/0000-0002-9469-401X

I.R. Romanchuk, Associate Professor, Department of Pediatrics and Pediatric Infectious Diseases, Bukovinian State Medical University. e-mail: romanchuk.lesia@bsmu.edu.ua; https://orcid.org/0000-0002-0676-3960

I.B. Schikar, Head of Pulmonology Department of the Regional Municipal Non-Profit Facility “Chemnitz Regional Children’s Clinical Hospital”, e-mail: innasichikarmak@gmail.com

B.I. Kshushin, Pediatric Anesthesiologist of the Highest Qualification Category, Infectious Department of Anesthesiology and Intensive Care of the Regional Municipal Non-Profit Facility “Chemnitz Regional Children’s Clinical Hospital”, e-mail: kshushin2201@icloud.com

Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Резюме. У разі виникнення коронавірусної хвороби (COVID-19) у дітей, які страждають на первинний імунодефіцит, останній може бути обтімнюючим чи пом’якшуючим фактором перебігу інфекції, що була спрямована на коронавірусом тяжкого гострого респіраторного синдрому-2 (SARS-CoV-2). Синдром WHIM (бородавки, гіпогаммаглобулінемія, інфекції та мієлокатексис) зазвичай класифікують як тяжку вроджену нейтропению, але більшість пацієнтів мають множинні дефіцити лейкоцитів, навіть панлейкопенію, і тому він також може бути класифікований як тяжкий комбінований імунодефіцит. В-лімфопенія особливо тяжка, і це, імовірно, частково пояснює гіпогаммаглобулінемію. Це рідкісне захворювання, спричинене автосомно-домінантними мутаціями, є комбінованим варіантом імунодефіциту, що включає мієлокатексис, сприйнятливість до інфекцій та гіпогаммаглобулінемію. Мієлокатексис є унікальною формою ациклічної тяжкої вродженої нейтропенії, спричиненої накопиченням зрілих і дегенеративних нейтрофілів у кістковому мозку. Виникають також моноцитопенія та лімфопенія, особливо В-лімфопенія. У деяких хворих спостерігаються вади розвитку серцево-судинної, сечостатевої та нервової систем, що в цілому може призводити до надзвичайно тяжкого перебігу інфекційного запального процесу, зокрема внаслідок SARS-CoV-2. Мета: проаналізувати клініко-лабораторні особливості перебігу коронавірусної хвороби, спричиненої SARS-CoV-2, у пацієнтів з імуносупресією на прикладі клінічного випадку COVID-19 у дитини з раніше діагностованим синдромом WHIM. Матеріали та методи. У статті представлено власні спостереження перебігу коронавірусної хвороби в дівчинки-підлітка з попередньо вирифікованим первинним імунодефіцитом (синдром WHIM) у період після хірургічної рутинної корекції відкритої артеріальної протоки. На 2-гу добу раптового початку захворювання дитина була госпіталізована в стані середньої тяжкості з ознаками запалення дихальних шляхів у вигляді ринофарингіту й обструктивного бронхіту. Результати. За результатами лабораторних досліджень встановлено лейкопенію, абсолютну нейтропенію, підвищення рівня прокальцитоніну, С-реактивного білка, D-димеру в сироватці крові та скорочення активованого часткового тромбопластинового часу. Лікування включало гідробалансну терапію перорально та інфузійно, системну та місцеву інгаляційну терапію коротким курсом стероїдів, антибактеріальну терапію цефалоспоринами IV покоління, внутрішньовенне введення гранулоцитарного колонієстимулюючого фактора й симптоматичне лікування. Стан дівчинки поступово покращувався, на 7-му добу вона була виписана зі стаціонару для продовження лікування в амбулаторних умовах. Висновки. Тяжкість респіраторної паатології та прогноз COVID-19 залежать від типу імунодефіциту і ураженої ланки імунної системи, а також від гетерогенності нових штамів SARS-CoV-2. Обтімнююча/захисна роль первинного імунодефіциту, зокрема синдрому WHIM, в узагальненій тяжкості COVID-19 наразі обмежена через невелику кількість спостережень і потребує подальшого збору даних. У представленому клінічному випадку описується класична середньо-тяжка коронавірусна інфекція дихальних шляхів у підлітка з первинним імунодефіцитом. Ключові слова: діти; коронавірусна хвороба COVID-19; респіраторні прояви; синдром WHIM