ACTA MEDICA SALINIANA

ORIGINAL PAPERS

HEMOLYTIC UREMIC SYNDROME IN A PEDIATRIC INTENSIVE CARE UNIT – RAPID REVIEW WITH CASE SERIES

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ISSN 0350-364X

DOI: 10.5457/701

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ABSTRACT

Hemolytic uremic syndrome (HUS) is a multiorgan clinical syndrome characterized by the simultaneous occurrence of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. This is the most important form of thrombotic microangiopathies in children and is considered the main cause of acute renal insufficiency in children, especially under the age of five. Over 90% of HUS in children is associated with infection, and the prodromal manifestation most often includes bloody diarrhea. Atypical hemolytic uremic syndrome (aHUS) is a rare but progressive, life-threatening condition that affects about 10% of HUS cases in children. It is predominantly caused by dysregulation of the alternative complement pathway and genetic predisposition. Conditions that enhance complement, such as some viral infections, malignancies, autoimmune diseases and transplantation may be comorbid in up to 70% of aHUS cases. The 2016 International Hemolytic Uremic Syndrome Group classification, based on the etiology, separates 4 groups: caused by infection, with coexisting conditions, due to cobalamin C disorders and due to complement dysregulation. Monoclonal antibody that effectively blocks complement activation, has significantly changed aHUS treatment and outcome. Early etiological recognition in order to start specific treatment as soon as possible is crucial for the outcome. This paper, through a rapid review and series of three children treated for HUS in our pediatric intensive care unit over a two-year period, aims to emphasize the complexity of the diagnosis and treatment of HUS, and the importance of a multidisciplinary team in order to to avoid complications, and achieve the best short- and long-term outcome.

Keywords: hemolytic uremic syndrome; pediatric intensive care, renal replacement therapy, plasmapheresis, ravulizumab.

INTRODUCTION

The simplest definition of hemolytic-uremic syndrome (HUS) indicates it as a multiorgan clinical syndrome characterized by the simultaneous occurrence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury (ARI) [1]. However, nothing about HUS is either simple or uniform. It belongs to thrombotic microangiopathies (TMA), a group of pathohistologically similar disorders that, in addition to HUS, most often includes thrombotic thrombocytopenic purpura (TTP), and a number of other conditions that must be excluded in the differential diagnosis. Primarily and for the longest time, TTP was investigated, since the first description by Eli Moschcowitz in 1924, so it was labeled as Moschcowitz disease for a long time [2]. The TTP pentad defined in 1966, in addition to the HUS triad (MAHA, thrombocytopenia, ARI), also includes fever and neurological symptoms, along with multiorgan microangiopathic lesions [3].

TMA is a life-threatening syndrome of systemic microvascular occlusions, these conditions have a similar clinical presentation of consumptive thrombocytopenia, mechanical hemolysis, and organ failure, but with different causes [4]. It belongs to the register of rare diseases, with an incidence of 3-5/100,000. There are some differences in the age of onset, HUS is more common in children, especially under 2 years of age, while TTP is more common in adults, and all TMAs occur more often in females [4]. These conditions were fatal until the 70s of the last century, when the revolutionary discovery of the importance of ADAMTS13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif-member 13) in the pathogenesis of TTP, known as the Furlan-Tsai hypothesis, significantly improved differential diagnostics , but also the treatment of all TMA, by discovering the beneficial effect of plasma therapy [2]. In the late

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Received:
26.07.2023.

Accepted:
6.9.2023.

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Funding: none

Competing interests: none

twentieth century, several studies identified ADAMTS 13 deficiency as a primary pathogenic cause of TTP [3]. The immediate application of plasma infusions and plasmapheresis reduced the mortality rate from about 90% to about 20% [2-4].

Hemolytic uremic syndrome (HUS) is the most important form of TMA in children because of its relative frequency and associated morbidity and mortality [5]. HUS is a very serious disease, with a fulminant course, an uncertain prognosis due to the high mortality rate, and is considered the main cause of ARI in children, especially under the age of five [6]. It is very important to distinguish the exact form of TMA as early as possible, because this determines the choice of specific treatment that should be started as soon as possible, already in the first hours [7]. Clinical manifestations of HUS are presented in Table 1.

Table 1. Clinical manifestations of HUS - typical HUS triad

Components of the HUS triad	Features
Microangiopathic hemolytic anemia (MAHA)	Microangiopathic hemolytic anemia
	Coombs negative
	Plasma LDH ↑
	Haptoglobin ↓
	Erythrocyte production ↑
	Intravascular hemolysis is the most sensitive marker for monitoring recovery
	The severity of the disease does not correlate with the clinical outcome
Trombocytopenia	Chaotic and short-lived
	It can be neglected
	Consumptive type of thrombocytopenia
	Platelets are taken up in the reticuloendothelial system
	Significant bleeding is rare
	Predominantly prothrombotic condition
Acute kidney injury (AKI)	It occurs suddenly
	Usually as sudden oligoanuria
	Possible proteinuria
	Frequent hypertension
	Manifestations are severe and difficult to treat in aHUS
	Typical HUS associated with infection is usually milder

Basic statistical data of HUS are presented in table 2.

Table 2. HUS statistical data

Important statistics	More information
HUS risk factors	Female gender, Severe colitis, Fever, Leukocytosis
	Younger age
	Antimotility agents, Antibiotics
	Alterations in the gene for factor H
	Implicated in the pathophysiology of atypical HUS
Magnitude of the problem	The most common cause of acute kidney injury in childhood
	Incidence 3-8/100,000 population in children aged 1-18 years
	Gradual decline from early childhood to adolescence
	Significant morbidity and mortality in the acute phase
Prognosis /outcome	Need for acute dialysis 50-70%
	Persistent renal injury 25% (hypertension, proteinuria, GFR↓)
	Primary diagnosis for 4/5 children on chronic RRT
	Serious extra-renal complications 20%
	Mortality 20-25%

Over 90% of HUS in children is associated with infection, most often gastroenteritis, designated according to the old classification as diarrheal d-HUS, i.e. post-infectious or typical HUS [8]. A minority of cases, in addition to being associated with infections, mainly have genetic or acquired changes in the alternative pathway of the complement system, called atypical HUS [9-11]. Shiga toxin-producing Escherichia coli (STEC-HUS) is typically the infectious agent, although HUS has also been reported following exposure to Shigella, Campylobacter, and Streptococcus pneumoniae. Post-infectious HUS can occur after a viral or bacterial infection, and the prodromal manifestation most often includes bloody diarrhea [12].

Atypical hemolytic uremic syndrome (aHUS) is a rare but progressive, life-threatening condition that affects both children and adults. It accounts for about 10% of HUS cases in children and the majority of HUS cases in adults [13]. It is predominantly caused by dysregulation of the alternative complement pathway and genetic predisposition to TMA precipitation and endothelial damage. Conditions that enhance complement, such as some viral infections (EBV, CMV, HIV), malignancies,

autoimmune diseases, transplantation, and pregnancy, activate the alternative complement pathway and may be comorbid in up to 70% of aHUS cases [14]. Common bacterial and viral infections, including Streptococcus pneumoniae, cytomegalovirus, H1N1 influenza, HIV, and parvovirus, may precede up to half of aHUS cases. They are associated with increased production of C5 [15].

A better understanding of the etiology and pathophysiology of HUS, achieved in the last decade, by interpreting the role of complement regulation, was the basis for the proposed new classification, instead of the traditional diarrhea-positive and -negative HUS. The 2016 International Hemolytic Uremic Syndrome Group classification, based on the etiology of HUS, separates 4 groups: as: 1) HUS caused by infection (STEC, Streptococcus pneumoniae, Influenza A, HIV); 2) HUS with coexisting conditions (transplantation, malignancies, autoimmune diseases, drugs, hypertension); 3) HUS due to cobalamin C disorders; and 4) HUS due to dysregulation of the alternative complement pathway [7]. The recent introduction of eculizumab, a monoclonal antibody that effectively blocks complement activation, has significantly changed the treatment and outcome of patients with aHUS [16]. Therefore, early etiological recognition of the disease in order to start specific treatment as soon as possible is crucial for the outcome.

The paper presents a series of three children treated for HUS in our pediatric intensive care unit (PICU) over a two-year period, with the aim of showing all the complexity of this rare pediatric emergency. The real question is how many specialties are needed to effectively treat these patients, which encourages the establishment of a broad multidisciplinary team, and suggests the establishment of national specialized centers for the treatment of all forms of HUS and TMA.

CASE SERIES

Case 1

Case 1 was an emergency transfer from the Infectious Disease Clinic, a male infant aged 10 months, with body weight (BW) 9.6 kg (50p), body height 80 cm (25p), after two days of unsuccessful treatment for gastroenteritis. He was admitted to the pediatric intensive care unit (PICU) with reduced consciousness, adynamic, dehydrated, extremely pale-yellow skin, edematous, hypertensive, giving the impression of severe illness, with hemorrhagic enterocolitis and signs of hepatorenal and anemic syndrome. In the first complete blood count, there was pronounced anemia (erythrocytes 2.9x1012/L; Hemoglobin 78 mg/L, hematocrit 0.21; platelets 26x109/L) with uremia (urea 23.7 mmol/L; serum creatinine - SCr 315 micromol/L). Due to the rapid progression of acute renal insufficiency (ARI), an indication for urgent hemodialysis (HD) was set, so, regardless of the risks, a dialysis central venous catheter (CVC) was urgently placed. Admission diagnoses were: acute hemorrhagic gastroenterocolitis, acute renal insufficiency, suspected hemolytic uremic syndrome.

Due to acute renal insufficiency and hypertensive crisis, an acute hemodialysis program was carried out for 9 days, along with treatment of hemolytic anemia (corticosteroids, IVIG, blood derivatives: fresh frozen plasma -FFP, cryoprecipitate, erythrocytes), diuretics, antihypertensives and other general supportive therapy. The patient was managed by a multidisciplinary team, the clinical condition, therapy and diagnostic tests were evaluated daily. Although only Rotavirus was confirmed by microbiological tests, based on clinical findings and diagnostic tests, the final diagnosis was a typical post-infectious form of hemolytic uremic syndrome (HUS). The course of the disease was favorable, stabilization and recovery were achieved with the treatment, he was discharged home on the 32nd day, with lower doses of corticosteroids and antihypertensives. He is still in remission, with regular follow-up.

Case 2

Case 2 was an emergency transfer from the local general hospital of a girl aged 13 months, body weight (BW) 10.3 kg (50p), body height 76 cm (25p), after two days of unsuccessful treatment for bloody gastroenteritis. She was admitted to the pediatric intensive care unit (PICU), with reduced consciousness, subfebrile, dehydrated, pale, edematous, giving the impression of severe illness. On admission, bloody diarrhea continued, she was oliguric to the point of anuria despite diuretics and other conservative treatment. On physical examination, she was generalized edematous, hytensive, extremely pale. In the first complete blood count, there was pronounced anemia (erythrocytes 2.3x1012/L; Hemoglobin 56 mg/L, hematocrit 0.16; platelets 86x109/L) with uremia (urea 18.6 mmol/L; serum creatinine - SCr 292 micromol/L). Due to the rapid progression of acute renal insufficiency (ARI), an indication for urgent hemodialysis (HD) was set, so, regardless of the risks, a dialysis central venous catheter (CVC) was urgently placed. Admission diagnoses were: acute hemorrhagic gastroenterocolitis, acute renal insufficiency, suspected hemolytic uremic syndrome.

Replacement of the dysfunctional dialysis catheter was complicated by severe hemorrhagic syndrome and respiratory failure, requiring immediate intubation and mechanical ventilation (MV), urgent replacement of multiple blood products. The girl was in an extremely difficult condition, requiring maximum multi-organ support, careful clinical supervision and control of biochemical parameters. She was still anuric, so the dialysis program was continued daily, with immunosuppressive therapy (corticosteroids, intravenous immunoglobulins - IVIG), blood derivatives as needed (fresh frozen plasma, cryoprecipitate, erythrocytes,), human albumin with diuretics, antihypertensives, etc. On the 7th day, she was weaned off MV, the dialysis program continued along with all other intensive medication treatment. A minimal diuresis was established from the 8th day and after 9 dialysis cycles a satisfactory diuresis was established, but the biochemical parameters were

still poor, maintaining unstoppable hemolytic activity, so the multidisciplinary team determined plasmapheresis. Staphylococcus in blood culture and Enterococcus in urine culture were confirmed, and antibiotic therapy was considered, selected and dosed with daily monitoring of clinical and laboratory parameters. She became febrile again on the 15th day, with confirmation of Candida sepsis, after antibiotic correction, the fever stopped after 3 days.

Despite significant clinical improvement, the disease was biochemically very active, so the multidisciplinary team decided to intensify immunosuppressive therapy with Azathioprine, pending the results of genetic tests and given that Eculizumab/Ravulizumab were not available. Azathioprine was discontinued after 5 days due to consequent agranulocytosis, and granulocyte colony-stimulating factor (G-CSF), Filgrastim was started, and leukocytes were normalized after 5 days of treatment. A period of gradual recovery followed, the CVC was removed on day 47, and the therapy was gradually de-escalated, while the final immunological and genetic results were awaited. She was discharged home recovered, is still in remission, with regular follow-up.

Case 3

Case 3 was an emergency admission from home, female child, age 15 months, body weight (BW) 13.6 kg (99p), body height 83 cm (99p), after five days of gastroenteritis, febrility, reduced diuresis, with the appearance of blood in the stool. He was admitted to the pediatric intensive care unit (PICU), with reduced consciousness, adynamic, dehydrated, extremely pale, edematous, giving the impression of severe illness. In the first complete blood count, there was pronounced anemia (erythrocytes 1.9x1012/L; Hemoglobin 47 mg/L, hematocrit 0.13; platelets 81x109/L) with uremia (urea 70 mmol/L; serum creatinine - SCr 817 micromol/L). Due to the rapid progression of acute renal insufficiency (ARI), an indication for urgent hemodialysis (HD) was set, so, regardless of the risks, a dialysis central venous catheter (CVC) was urgently placed. Admission diagnoses were: acute hemorrhagic gastroenterocolitis, acute renal insufficiency, suspected hemolytic uremic syndrome.

According to the course of the disease and response to treatment (dialysis, plasmapheresis, corticosteroids, IVIG, blood products, diuretics, antihypertensives, Filgrastim, etc.), an atypical form of HUS was suspected from the beginning. Additional genetic testing was immediately undertaken and preliminary results confirmed the diagnosis, so the multidisciplinary team prescribed treatment with complement inhibitor monoclonal antibodies, according to the protocol. Simultaneous immunization with pneumococcal and meningococcal vaccines was performed, as prescribed by the Eculizumab therapy protocol.

The disease presented in full severity, the child still required daily hemodialysis, which maintained biochemical parameters within acceptable limits, but clinically she was without improvement, extremely edematous, anuric, hypertensive, with purpura, with threatening pulmonary edema. Biochemically, significant thrombocytopenia, hemolytic anemia and other disease activity parameters were maintained, with constant variations in other biochemical findings, and the need to adjust intensive treatment.

From the 60th day of hospitalization, despite the treatment, she was in critical condition, with hemorrhagic syndrome and pulmonary edema, she was intubated, on MV, with analgosedation, relaxation, inotropes. This was followed by a further deterioration of the cardiovascular status, a weakening of the myocardial tone, requiring the intensification of the dialysis program, and due to the massive pulmonary hemorrhage, all complex treatment and substitutions with blood derivatives were intensified. Tracheobronchial lavage with pulmonary surfactant was performed on several occasions. The general condition was getting worse, she had unstable vital functions, with unresolved pulmonary edema and hemorrhagic syndrome. She required maximum supportive therapy, continuation of the intensive dialysis program with resuscitation procedures. Despite all the actions, there was no response. Exitus lethalis was declared on the 86th day of hospitalization.

DISCUSSION

HUS belongs to the register of rare diseases with an incidence of 0.7-8 cases per year per 100,000 inhabitants of a certain region, with considerable geographic and seasonal variability [17-20]. Our clinic and PICU covers the area of Tuzla Canton, where, out of a total of 650,000 inhabitants, children under the age of 18 participate with about 100,000. Three cases of HUS in a two-year period, treated in our PICU, are in accordance with the reported incidence, and they confirm its rare disease status. Regionally, the cases came from the northern, lowland areas of the canton, and seasonally, all cases were recorded at the end of winter. The age of all three children was about one year, they were two girls and one boy. This is pretty much in line with published reports.

The onset of the disease in all three cases was almost identical, it started with diarrhea, until bloody stools, and the children did not get better despite the treatment. According to the literature, HUS is usually preceded by infectious gastroenteritis [21]. Symptoms are nonspecific, including nausea, abdominal pain, and diarrhea that is initially watery but becomes bloody in more than 70% of cases within 2–3 days [1, 5]. Although STEC HUS is considered the most common form in children, STEC gastroenteritis is generally a mild disease in 85-90% of cases, with full recovery [6-8]. Complications are rare, and the most serious is HUS, which develops in 10-15% of patients after 7-10 days from the onset of symptoms [7]. According to the literature, in most cases, HUS manifests suddenly with reduced urine output and edemas [22], as in our cases. Initial clinical manifestations may indicate, but only basic laboratory tests and the characteristic triad of devia-

tions provide a working diagnosis [7]. In our examples, the combined findings of hemolytic anemia, thrombocytopenia, and uremia were immediately highly suggestive of HUS as a pediatric emergency, a multiorgan disease, with rapid, significant acute kidney injury. Clinical characteristics, therapy, and outcome of HUS patient series are presented in table 3.

Table 3. Clinical presentation, therapy, and outcome of HUS patient series

Patient	No. 1	No. 2	No. 3
Age (months)	10	13	15
Gender	male	female	female
Weight (kg)	9.6	10.6	13.6
Height (cm)	80	76	83
Hb (g/dl)	7.8	5.6	4.7
Thrombocytes (/nl)	26	86	81
Creatinine (micromole/l)	315	292	817
Urea (mmol/l)	23.7	18.6	70
Direct Coombs test	negative	negative	negative
genetic tests	no	Yes, negative	Yes, positive
corticosteroids, IVIG	yes	yes	yes
Azathioprine	no	yes	no
Filgrastim	no	yes	yes
Dialysis duration (days)	9	9	86
plasmapheresis	no	yes	yes
ravulizumab	no	no	yes
mechanical ventilation (days)	-	7	27
recovery	yes	yes	no
sequels	hypertension	hypertension	-

A rare form of postinfectious HUS caused by streptococcus pneumoniae, which usually occurs after respiratory infections, may also begin with diarrhea [23, 24]. Atypical HUS, as the most severe form, the most difficult to treat, can also begin with diarrhea, which complicates the etiological differential diagnosis [25-27]. According to the literature, only a third of patients have a recognizable etiology, the most common of which is STEC-HUS, and it represents half of the cases with a known etiology [1].

Our case 1 was concluded as STEC HUS, mostly because it responded well to intensive therapy, while it was not confirmed microbiologically, because only Rotavirus was isolated. Cases 2 and 3 did not respond well to intensive treatment, which greatly increased the suspicion of atypical HUS, so additional tests, including genetics, were immediately undertaken.

In all three cases, renal replacement therapy (RRT) and therefore urgent positioning of a dialysis central venous catheter (CVC) was required, despite all the risks (Figure 1).

Due to extremely severe and very sudden illness, in addition to immediate general intensive supportive treatment, all of them required continuous renal replacement therapy (RRT), and specific therapy options which included fresh frozen plasma (FFP), immunosuppressants, intravenous gammaglobulins, optionally plasmapheresis and Eculizumab. From the beginning, a multidisciplinary team was involved in the treatment of these critically ill children, which was crucial for their outcome. A multidisciplinary team (pediatrician, intensivist, nephrologist, hematologist, immunologist, clinical pharmacologist, cardiologist, pediatric surgeon, neurologist, infectious disease specialist, transfusiologist, clinical geneticist and others) constantly considered and monitored the clinical condition and parameters of anemia, thrombocytopenia, hemolysis, uremia, with monitoring of coagulation status, albumin, electrolytes, acid-base status, parameters of inflammation, microbiological, immunological findings, with regular controls of multiorgan involvement (ultrasound examination of the abdomen, kidneys, heart, lungs), chest x-ray (Figure 2), ECG monitoring, fundus examination and others.

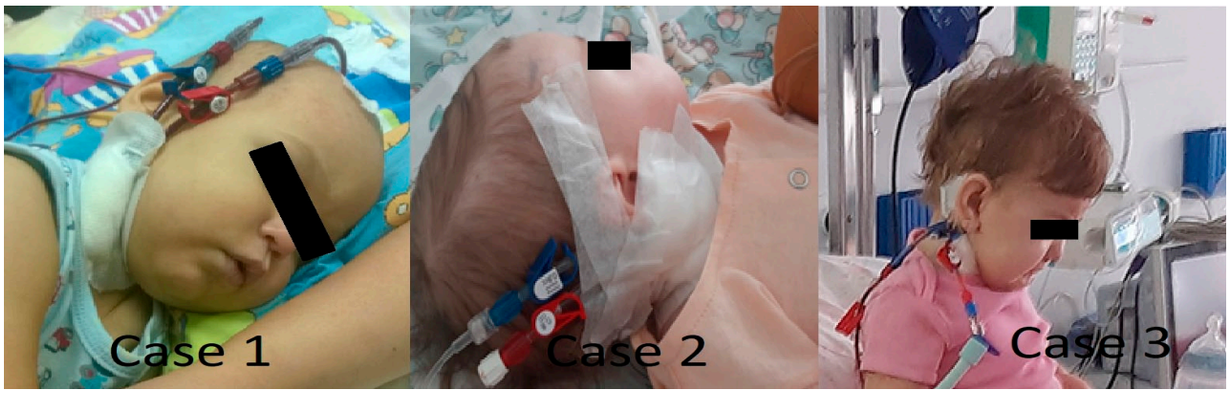

Figure 1. Central venous dialysis catheters in a case series

As reported by recent literature, RRT is needed in 50-70% of cases in the acute phase of HUS [21, 22], without proven advantages of a certain type of RRT, therefore it should be selected in line with the experience of the specific medical center, and personalized according to the patient's condition.

Timely management of HUS is the most important outcome factor. The turning point in the treatment of TMA, several decades ago, was the introduction of plasma therapy and plasmapheresis, which must be started in the first hours, then immunosuppressive therapy was improved, and in the last decade, treatment has been revolutionized with biological therapy, especially for atypical HUS [7]. In high-resource countries, specialized centers for the treatment of TMA, with multidisciplinary teams, are being developed, so it is crucial to recognize type of HUS in time and refer the patient to a specialized center as soon as possible, to ensure optimal treatment [8]. Reports demonstrate better patient outcomes after the introduction of multidisciplinary teams for the treatment of HUS and other TMAs.

Therefore, the treatment is complex, with numerous possible complications. There were the least of them in case 1, which required very careful continuous RRT for a full 9 days, in addition to all other treatments, after which the desired improvement was visible. In case 2, the repositioning of the dialysis CVC was complicated by a marked hemorrhagic syndrome and marked general deterioration, necessitating a significant intensification of the overall treatment, but fortunately, continuous RRT was able to continue. Case 3 was very complicated from the beginning, and very resistant to therapy, and due to long-term daily continuous RRT, there was a need for multiple re-placement of dialysis CVCs. Except for case 1, the other cases required longer mechanical ventilatory support, as noted on radiological images of these patients (Figure 2).

Case 1 did not require plasmapheresis, and was treated with transfusions of fresh frozen plasma (FFP) along with corticosteroids, intravenous immunoglobulin (IVIG) and all other general supportive therapy. In case 2, continuous RRT, FFP transfusions, corticosteroids, IVIG and all other general supportive therapy, did not immediately achieve a good response. Diagnostics was quickly directed towards atypical HUS, with plasmapheresis executed. According to the knowledge, genetic testing additionally identifies the etiologies of HUS and affects prognosis, as it confirms patients with dysregulation of the complement pathway, who require treatment with monoclonal antibodies as soon as possible [15, 16]. Recently, two monoclonal antibodies for the treatment of atypical HUS have been approved in our country: eculizumab and ravulizumab. As the genetic tests in case 2 were negative, biological therapy was not carried out. The disease itself, as well as the applied therapy, additionally affect immune status, so the risk of new attached infections is very high. In our case 2, Candida sepsis was confirmed (and successfully treated), which is not surprising given all recorded risk factors for fungal infection. [28].

Case 3 was very difficult from the beginning, very resistant to all the treatment prescribed by the multidisciplinary team. The initial suspicion of atypical HUS was definitively confirmed by genetic tests. Ravulizumab therapy was started immediately according to the protocol, but, unfortunately, even that did not change the course of the severe disease. This is inconsistent with the reported significant improvements in the course and outcome of aHUS after monoclonal antibody treatment [10, 16]. This suggests a possible combined etiology, along with a genetic background, which made this form of aHUS very resistant to all treatment options. Our data confirm all the complexity of the aHUS problem. It is definitely a tricky multiorgan disease, with multiple and often mysterious etiology, often resistant to available treatments.

Available data reveal that most patients recover kidney function, but 25% develop sequelae, most commonly hypertension, proteinuria, and chronic kidney disease (CKD) [27]. Our two survivors were monitored and treated for hypertension for several months after recovery. Patients with HUS require long-term follow-up, mostly by a pediatric nephrologist, since CKD can occur even after several years [21, 22]. Children are considered to have a large renal functional reserve, because preserved nephrons can compensate for the function of damaged ones. Careful monitoring is necessary in

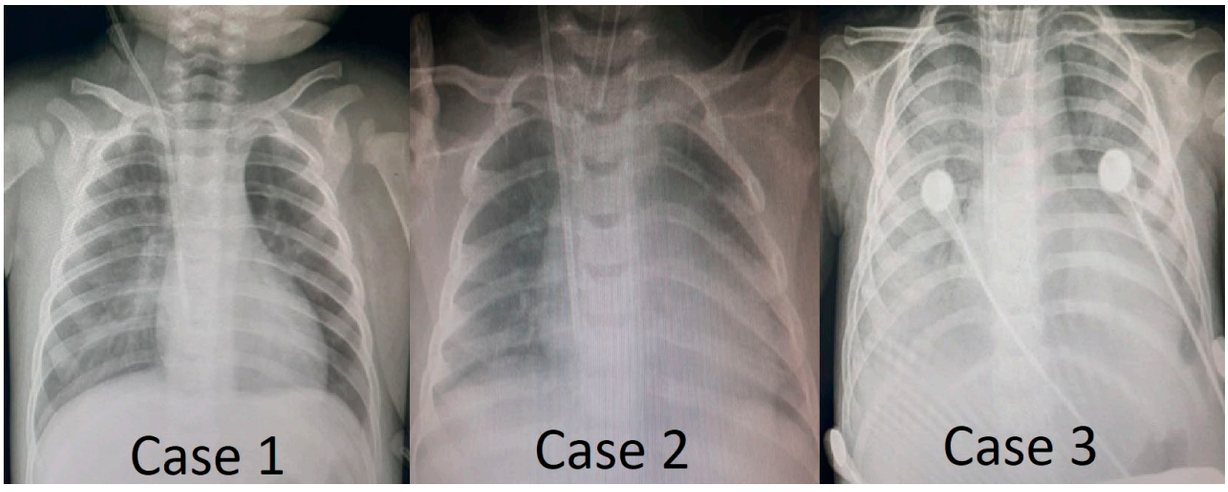

Figure 2. Chest X-ray of patients

order to recognize changes and apply available kidney protection strategies in time.

CONCLUSION

This series confirms HUS as a pediatric emergency, a very severe and unpredictable multisystem disease. For optimal patient outcomes, early recognition and timely initiation of appropriate treatment are critical in attempting to reduce the risk of irreversible organ damage or death. Although in the last two decades there has been significant progress in the diagnostic and therapeutic approach of patients with HUS, atypical HUS, as the most severe form, remains a diagnostic and therapeutic challenge. Therefore, for each individual patient, the target treatment should differentially exclude or confirm aHUS, since the start. The implementation of a multidisciplinary team is necessary in order to define the diagnosis faster and more efficiently, and as the treatment of the disease becomes more complex, it is important to engage all key professionals and groups in making urgent clinical decisions for individual patients. Centers that can provide quality PICU treatment, advanced RRT options, and detailed etiologic investigations, including genetic testing, should also be developed. Long-term follow-up is required, even in HUS patients who appear to have fully recovered from the acute phase.

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