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Evaluation of Pediatric Invasive Bacterial Infections After the COVID-19 Pandemic

COVID-19 Pandemisi Sonrası İnvaziv Bakteriyel Enfeksiyonların Değerlendirilmesi

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Abstract

Objective: Invasive bacterial infections are among the most common causes of mortality and morbidity all over the world. With this study, it was aimed to evaluate pediatric invasive bacterial infections seen with the relaxation of COVID-19 pandemic measures.

Material and Methods: Twenty-five children who were followed up in Eskişehir Osmangazi University Faculty of Medicine Hospital between December 2022 and February 2023 with the diagnoses of pulmonary effusion/empyema, bacteremia, mastoiditis, and toxic shock syndrome were included in the study. The clinical, epidemiological and laboratory findings of the cases were evaluated.

Results: Of the twenty-five children included in the study, 13 (52%) were boys and the median age of the study population was 70 (9-204) months. Pleural effusion/empyema was diagnosed in 16 (71%), mastoiditis in seven, bacteremia in eight, and toxic shock syndrome in two cases. Pathogenic microorganisms were identified in at least one culture and multiplex polymerase chain reaction (PCR) test in fifteen cases. While only medical treatment was given to eight cases, surgical and medical treatment was applied to 17 cases. Thirteen patients needed critical care. The average hospital stay was 12 (4-26) days, and one patient died during hospitalization.

Conclusion: Invasive bacterial infections especially the incidence rates of cases with invasive Group A streptococcal infection (iGAS) have increased after the pandemic. Early recognition of cases and initiation of appropriate treatment in the early period are of critical importance. For this reason, both health professionals and the society should be informed about the disease and its early findings.

Keywords: Bacteremia, pandemics, pediatrics

Öz

Giriş: İnvaziv bakteriyel enfeksiyonlar, tüm dünyada en yaygın mortalite ve morbidite nedenleri arasında yer almaktadır. Bu çalışma ile COVID-19 pandemi önlemlerinin gevşetilmesi ile birlikte görülen pediyatrik invaziv bakteriyel enfeksiyonları değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Aralık 2022-Şubat 2023 tarihleri arasında Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Hastanesinde pulmoner efüzyon/ampiyem, mastoidit ve toksik şok sendromu tanılarıyla izlenen 25 çocuk çalışmaya alındı. Olguların klinik, epidemiyolojik ve laboratuvar bulguları değerlendirildi.

Bulgular: Çalışmaya alınan 25 çocuktan 13 (%52)'ü erkekti ve medyan yaşları 70 (9-204) aydı. On altı (%71) olguda plevral efüzyon/ampiyem, yedi olguda mastoidit, sekiz olguda bakteriyemi ve iki olguda toksik şok sendromu saptandı. Vakaların 15'inde en az bir kültür ve multipleks PCR testinde patojen saptandı. Sekiz olguya sadece medikal tedavi uygulanırken 17 olguya cerrahi ve medikal tedavi uygulandı. On üç hastanın yoğun bakıma ihtiyacı vardı, ortalama hastanede kalış süresi 12 (4-26) gündü ve eksitus olan bir olgu vardı.

Sonuç: İnvaziv bakteriyel enfeksiyonlar özellikle invaziv Grup A streptokok (iGAS) vakaları pandemi sonrasında görülen ve morbidite ve mortalitesi yüksek enfeksiyonlardandır. Vakaların erken tanınması ve uygun tedavinin erken dönemde başlanması kritik öneme sahiptir. Bu nedenle hem sağlık profesyonelleri hem de toplum hastalık ve erken bulguları hakkında bilgilendirilmelidir.

Anahtar Kelimeler: Bakteriyemi, pandemi, pediyatri

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Introduction

Invasive bacterial infections are leading causes of global morbidity and mortality among all age groups, especially among young children aged <5 years, adolescents, and older adults aged >65 years. The most common pathogenic agents identified in these life-threatening infections are *Streptococcus pneumoniae,* nontypeable *Haemophilus influenzae* (NTHi), *Neisseria meningitidis* and *Streptococcus pyogenes,* which normally live in the nasopharynx or throat of healthy individuals and are transmitted person-to-person via the respiratory route. Respiratory infections were the sixth leading cause of death among all ages and the most common cause of death in children younger than five years (1). There were 336 million episodes of lower respiratory infections worldwide, leading to 2.4 million deaths (2,3).

In March 2020, World Health Organization (WHO) declared COVID-19 as a pandemic, and to control this pandemic, measures such as isolation and social distancing were first started to be enforced all over the world because at the beginning of the pandemic, there was no vaccine or treatment to prevent this pandemic. These non-pharmaceutical interventions including stay at home order, widespread mandatory use of face masks, canceling mass gathering activities, and mandating social distancing, school closures, and travel restrictions were implemented in countries around the world (4). Mitigation measures taken globally to reduce the spread of SARS-CoV-2 and the impact of COVID-19 have also reduced the transmission of other respiratory viruses and bacteria, including influenza virus A/B, respiratory syncytial virus (RSV), *S. pneumoniae,* NTHi, *N. meningitidis* and GAS which are frequently detected in children and also in many nosocomial infections (5-11). Ullrich et al. have evaluated the impact of the COVID-19 pandemic and the associated non-pharmaceutical interventions on notifiable infectious diseases in Germany and have shown that the interventions resulted in a significant decrease in the incidence of infectious diseases, including tuberculosis, chickenpox, invasive meningococcal disease, seasonal influenza, and whooping cough (7).

After relaxation of isolation precautions, and social activity restrictions, re-opening of schools and kindergartens, reports of these viral and bacterial infections increased again (12). Increases in bacterial infections due to *S. pneumoniae*, NTHi, *N. meningitidis*, especially GAS, have been reported from all over the world, especially in England (13-20). Similar to the literature data, we saw consecutive twenty-five cases with bacterial infections such as pleural effusion/empyema, bacteremia, mastoiditis in our clinic between December 2022 and February 2023. The incidence rates of these diseases in our hospital were relatively high when especially compared to the pre-pandemic period. However, during the same time interval before the pandemic i.e. between December 2019 and February 2020, only five cases of invasive bacterial infections were seen, including three cases with pleural effusions and two cases with mastoiditis. Therefore, we decided to conduct this study so as to evaluate the clinical and epidemiological features, laboratory and radiologic findings of these pediatric cases of invasive bacterial infection.

Materials and Methods

After the pandemic, we found an increase in the incidence rates of invasive bacterial infections in our clinic, especially between December 2022 and February 2023. Therefore, twenty-five children who were followed up at Eskişehir Osmangazi University Faculty of Medicine Hospital between December 2022 and February 2023 with the diagnoses of pulmonary effusion/empyema, bacteremia, mastoiditis, and toxic shock syndrome were included in the study. The clinical, epidemiological and laboratory findings of the cases were evaluated. Blood, pleural fluid and sterile body fluid culture and throat culture results of the cases were recorded. Glucose, lactate dehydrogenase (LDH), protein, pH tests, culture and multiplex polymerase chain reaction (PCR) results from pleural fluid samples were evaluated. We used the Biofire Filmarray Pneumonia panel plus (Biomcerieux, France) kits, targeting 27 pathogens and seven antimicrobial resistance genes. Light's criteria were used for the distinction of transuda/exudate and for the diagnosis of empyema. Pleural effusion protein/serum protein> 0.5, pleural effusion LDH/serum LDH> 0.6, pleural effusion LDH> 2/3 of the upper limit of normal serum LDH (LDH> 200 IU/L) values were accepted as the criteria for differential diagnosis. If at least one of these criteria was present, it was considered as exudate. For empyema glucose <40 mg/dL, LDH> 1000 IU/L, pH< 7.2 were accepted as diagnostic criteria. For the diagnosis of toxic shock syndrome, demonstration of the presence of *S. pyogenes*, fever, involvement of at least two systems (renal, liver, cogulopathy, rash) and hypotension were accepted as diagnostic criteria. Exemplary cases are illustrated in Figures 2 and 3. Medical and surgical treatment regimens of the cases were evaluated. The study was started after the approval of the ethics committee of Eskişehir Osmangazi University Faculty of Medicine Hospital (Date: 06.01.2022, Number: 31).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 28.0 for Windows (SPSS, Chicago, IL, USA) was used for the statistical analysis. Continuous variables were expressed as median (minimum-maximum). Categorical variables are shown as percentage.

Results

Twenty-five children, including 13 (52%) boys and 12 (48%) girls, were enrolled in the study. Median age of the study population was 70 (9-204) months. Twenty-two (88%) patients

were previously healthy, the other patients had autoimmune hepatitis (n= 1), spinal muscular atrophy (SMA) (n= 1), and had undergone cochlear implant operation 12 months previously. A foreign national patient had never been vaccinated before. All of the cases had a history of oral/systemic antibiotic use prior to admission. Pleural effusion/empyema was diagnosed in 16 (64%), mastoiditis in seven, bacteremia in eight, and toxic shock syndrome in two cases. The most common symptoms at presentation were fever (100%), cough (64%), respiratory distress (57.1%), chest pain (32%) and otalgia (28%). Leukocytosis was detected in 76%, and acute phase reactant elevation in 92% of the cases (Table 1). All sixteen cases with pleural effusion were evaluated as parapneumonic effusion (Figure 1). Pleural fluid could be aspirated from twelve of the sixteen cases with pleural effusion. Pleural fluid was purulent in 10 (90%), and hemorrhagic in two (18%) cases. According to Light's criteria, all of these eleven pleural fluid samples were exudate and nine of them were empyema. Pathogens were identified in at least one culture and multiplex PCR tests in fifteen of the cases. The characteristics of the cases and the distribution of pathogenic bacteria are given in Table 2. In the serogroup determination of two cases of *H. influenzae,* NTHi was identified. Typing result is awaited in one case with *S. pneumoniae*. While only medical treatment was given to eight (32%) of 25 cases, surgical and medical treatment was applied in combination to 17 (68%) cases. Sixteen cases with pleural effusion/empyema underwent either only medical treatment (n= 5), tube thoracostomy (n= 6) or thoracotomy and decortication (n= 5). Fibrinolytic therapy was not given to any of the cases. Mastoidectomy and medical treatment were applied together in all seven cases diagnosed with mastoiditis. Facial nerve paralysis (pathogen *S. pneumoniae*) was present in two of seven cases diagnosed with mastoiditis, and sinus vein thrombus (pathogen GAS) was present in two patients (Figure 2). Only medical treatment was applied to two patients with the diagnosis of toxic shock syndrome (Figure 3). The most commonly used antimicrobial agents were ceftriaxone/cefotaxime, vancomycin, meropenem and clindamycin in decreasing rates. Clindamycin was added to the treatment of all eight cases in which GAS was detected by culture and multiplex PCR. Thirteen patients needed critical care, median hospital stay was 12 (range= 4-26) days, and one patient died during hospitalization (Tables 1,2).

Discussion

In our study, we found that there was an increase in the incidence of invasive bacterial infections in the post-pandemic period, especially compared to the pre-pandemic period. Indeed during the pre-pandemic period extending from December 2019 to February 2020, five cases of invasive bacterial infections were seen, including three cases of pleural effusions, and two cases of mastoiditis. In our study, the most common pathogen identified in cases of invasive bacterial infection was *S. pyogenes*. Guy et al. reported that there was a significant increase in invasive group A streptococcal (iGAS) infections in children under 15 years of age in England in November 2022, compared to the previous season, and 14 cases were lost (13). However in the previous season, *S. pyogenes* was reported in blood cultures in 87% and in lower respiratory tract aspirates in 5% cases. Whereas in November 2022, the incidence of lower respiratory tract infections increased to 28%. Similarly, in our study, GAS was detected in the pleural fluid in five of nine cases. B de Gier et al. reported that in the Netherlands, the incidence of iGAS infections in children increased seven times compared to pre-pandemic period (14). They also reported an increase in cases of toxic shock syndrome and necrotizing fasciitis compared to other causes of iGAS infection, and varicella zoster coinfection in seven of the cases. In our study, two cases had toxic shock syndrome and varicella zoster coinfection was not seen. The absence of varicella zoster infections in our cases compared to the data reported from Netherlands, can be explained by the fact that the varicella vaccine is included in the mandatory routine vaccination schedule in our country. The increase in the incidence of iGAS infections after the COVID-19 pandemic can be explained by the fact that people are not exposed to respiratory pathogens and cannot develop herd immunity against the pathogen as a result of the use of masks and social restrictions required during the pandemic period.

Bertran et al. have reported an increase in the incidence of invasive pneumococcal infections (IPDs) with the relaxation of isolation measures and emphasized the importance of immunization with pneumococal conjugate vaccine (PVC13) (15). Casonova et al. have reported that with the reduction of pandemic measures in Switzerland, cases of IPD increased, especially non-vaccine 23B pneumococcal serotypes and penicillin- resistant strains (16). In our study, *S. pneumoniae* was detected in the cultures of two cases of mastoiditis and one case with parapneumonic pleural empyema. Two samples were sent to the reference laboratory for serogroup typing. Typing could not be done in one case and the result of one case is awaiting.

Steens et al. reported that at the end of the first year of the pandemic in the Netherlands, the incidence of invasive pneumococcal and meningococcal infections decreased, while the incidence of *H. influenzae* vaccine-preventable serotype b (Hib) increased compared to the prepandemic period. They also emphasized the importance of case reporting and national surveillance studies (18). Kitano et al. reported an increase in the number of invasive *H. influenzae* cases, with a decrease in vaccination rates with the closure during the pandemic period, and emphasized that its incidence can be reduced with a rapid increase in

Table 1. Clinical and epidemiological features of the cases

Age, median (range) months	70 (9-204)
	n= 25 (%)
Gender	
Female	12 (48)
Male	13 (52)
Chronic diseases	3 (12)
Diagnoses	
Pleural effusion/empyema	16 (64)
Mastoiditis	7 (28)
Bacteremia	8 (32)
Toxic shock syndrome	2 (8)
Symptoms	
Fever	25 (100)
Cough	16 (64)
Dyspnea	14 (56)
Chest Pain	8 (32)
Otalgia	7 (28)
Leukocytosis	19 (76)
APR↑	23 (92)
Pleural fluid findings	11
Purulent	10 (91)
Hemorrhagic	2 (18)
Exudate	11 (100)
Empyema	9 (81)
Pathogens (identified by both culture and multiplex PCR)	15
S. pyogenes	8 (32)
S. pneumoniae	3 (12)
H. influenzae	2 (8)
S. epidermidis	1 (4)
E. coli	1 (4)
Pathogens (identified by culture)	11
S. pyogenes	4 (36)
S. pneumoniae	3 (27)
H. influenzae	2 (18)
S. epidermidis	1 (9)
E. coli	1 (9)
Pathogens (identified by multiplex PCR)	10
Pleural Fluid	9 (90)
S. pyogenes	5 (50)
S. pneumoniae	2 (20)
H. influenzae	1 (10)
E. coli	1 (10)
Abscess	1 (10)
S. pyogenes	1 (10)
Treatment	
Medical treatment	8 (32)
Surgical and medical treatment	17 (68)
Surgical treatment	17 (68)
Mastoidectomy	6 (24)
Tube thoracostomy	6 (24)
Thoracotomy and decortication	5 (23)
Patients hospitalised in the intensive care unit	13 (52)
Length of hospital stay (days) (median, range)	12 (4-26)

APR: Acute phase reactant, LDH: Lactate dehydrogenase, PCR: Polymerase chain reaction.

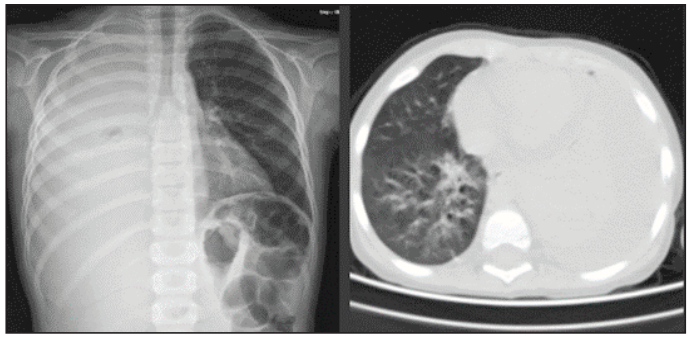

Figure 1. X-ray and thorax CT Images of a 10-year-old boy with pleural effusion.

the vaccination rate (19). Altuntaş et al., and Dinleyici et al. emphasized the importance of childhood vaccinations during the pandemic period in their studies (21-22). In our study, *H. influenzae* was detected in the pleural fluid samples of two cases. As a result of serogroup typing, contrary to literature data, NTHi was detected, rather than *H. influenzae* vaccine-preventable serotype-b (Hib). This fact can be explained by the high vaccination rate as a result of the devoted and self-sacrificing efforts of healthcare professionals, despite all the difficulties during the pandemic period in our country.

Centers for Disease Control and Prevention (CDC) and European Center for Disease Prevention and Control (ECDC) published a report on increased rates of invasive infections (especially iGAS infections) after the pandemic and emphasized the importance of early recognition of invasive infections, initiation of preventive measures and early treatment (23-24). Information and training programs were held in many European countries such as England, the Netherlands, Switzerland, and Spain. In our country, information for the public was provided both by the Ministry of Health and by social media. Seminars on the diagnosis and treatment of invasive infections were organized for healthcare professionals. In these seminars and information meetings, the importance of surveillance of vaccine-preventable invasive infections and their reporting was emphasized.

In our study, nine pathogens were detected from the pleural fluid samples by multiplex PCR method, while only four of these pathogens could be cultured. This finding can be explained by the fact that all of the cases had taken oral/systemic antibiotics before and the pathogen detection rates using multiplex PCR methods were higher than those identified by antimicrobial susceptibility tests performed in culture medias. New molecular diagnostic methods such as multiplex PCR have advantages such as rapid yields, identification of viral and bacterial multiple agents with a single test, and detection of antibiotic resistance mechanisms compared to conventional methods. The disadvantages of molecular methods are that they are expensive, do not distinguish between active infection and colonization, and their false positivity rates (25,26).

The main limitation of our study is that it was a single-center cross-sectional study and included a small number of cases within a short period of time. In addition, although it is a cross-sectional study, the characteristics of the cases before and after the pandemic could not be compared. Another limitation is that not all pathogens were grown in culture and subgroup determination could not be made.

Conclusion

In conclusion, invasive bacterial infections such as pleural empyema/effusions and mastoiditis, especially iGAS infections are common infections after the pandemic. Early recognition of cases and initiation of appropriate treatment in the early period are of critical importance. For this reason, both health professionals and the society should be informed about the disease and its early findings. In this way, it should be ensured that families apply to the hospital and culture samples be taken at an early stage and appropriate treatment should be started as soon as possible. Reporting invasive infections to the departments of national surveillance of vaccine-preventable invasive infections is of vital importance in the regulation of national and global health policies, implementation of the guidelines concerning the diagnosis and treatment of these infections and vaccination programs.

Ethics Committe Approval: The approval for this study was obtained from Eskişehir Osmangazi Unversity Non-Invasive Clinical Research Ethics Committee (Decision no: 31, Date: 06.01.2022).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - YK, MCK, EÇD, ÖK, GB, EK, MSA, ÖK, TU, MÖP; Design - YK, EÇD, MCK, ÖK; Supervision - EÇD, ÖK,; Resource - YK, MCK, GB, ÖK, MSA, ÇÖ, MÖP, TU, ÖK, EÇD; Data Collection and/or Processing - YK MCK, EÇD, ÖK, TU; Analysis and/or Interpretation - YK, MCK; Literature Search - YK, MCK, ÖK, EÇD, GB, EK, MÖP; Writing - YK, MCK, GB, EK, MSA, ÇÖ, MÖP; Critical Review – EÇD, ÖK, MÖP.

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Table 2. Clinical and demographic data of all cases

Case no	Age (month)	Sex	Diagnoses	Pathogens identified by culture	Pathogens identified by multiplex PCR	Surgical treatments and antibiotherapies	Hospitalization (PICU/Service)	Duration (day)
Case-1	37	F	Pleural empyema	-	*S. pyogenes*	Thoracotomy and decortication Meropenem + Vancomycin + Clindamycin	PICU	14
Case-2	48	M	Pleural effusion	-	*S. pyogenes*	Tube thoracostomy Ceftriaxone + Vancomycin + Clindamycin	PICU	13
Case-3	72	M	Pleural empyema	-	-	Tube thoracostomy Ceftriaxone + Vancomycin	PICU	10
Case-4	125	F	Pleural effusion	-	-	Ceftriaxone + Vancomycin + Clarithromycin	Service	9
Case-5	52	F	Pleural empyema	-	-	Tube thoracostomy Ceftriaxone + Vancomycin	PICU	10
Case-6	128	F	Pleural effusion	-	-	Ceftriaxone + Vancomycin + Clarithromycin	PICU	9
Case-7	204	F	Pleural effusion	-	-	Ceftriaxone + Vancomycin + Clarithromycin	Service	7
Case-8	34	F	Mastoiditis	*S. pneumoniae* (Abscess culture)	-	Mastoidectomy Piperacillin-tazobactam	Service	14
Case-9	82	M	Mastoiditis	-	-	Mastoidectomy Piperacillin-tazobactam	Service	21
Case-10	37	F	Pleural Empyema	*S. pyogenes* (Throat culture)	*S. pyogenes*	Tube thoracostomy Ceftriaxone + Clindamycin	PICU	9
Case-11	132	F	Pleural Effusion	-	-	-Ceftriaxone + Clarithromycin	Service	5
Case-12	72	M	Mastoiditis	*S. epidermidis* (Abscess culture)	-	-Ceftriaxone + Metronidazole	Service	10
Case-13	96	F	Pleural Empyema	-	*S. pyogenes*	Tube thoracostomy Meropenem + Vancomycin + Clindamycin	PICU	15
Case-14	50	M	Pleural Empyema Bacteremia	*H. influenzae* (Blood and pleural fluid)	*H. influenzae*	Thoracotomy and decortication Ceftriaxone + Vancomycin	PICU	17
Case-15	62	M	Mastoiditis Bacteremia	*S. pyogenes* (Blood)	-	Mastoidectomy Meropenem + Vancomycin + Clindamycin	Service	21
Case-16	68	F	Pleural Empyema -Bacteremia	*H. influenzae* -*Streptococcus pneumoniae* (Blood and pleural fluid)	*H. influenzae* *S. pneumoniae*	Thoracotomy and decortication Meropenem + Vancomycin + Clindamycin	PICU	26
Case-17	33	M	Pleural effusion	-	-	Thoracotomy and decortication Ceftriaxone + Vancomycin	PICU	18
Case-18	9	M	Pleural effusion	-	-	Ceftriaxone + Vancomycin	Service	10
Case-19	39	F	Pleural empyema	-	-	Thoracotomy and decortication Meropenem + Vancomycin + Clindamycin	PICU	14

Table 2. Clinical and demographic data of all cases (continue)

Case no	Age (month)	Sex	Diagnoses	Pathogens identified by culture	Pathogens identified by multiplex PCR	Surgical treatments and antibiotherapies	Hospitalization (PICU/Service)	Duration (day)
Case-20	44	M	Mastoiditis Bacteremia	*S. pneumoniae* (Blood and abscess)		Mastoidectomy Ceftriaxone + Vancomycin	Service	15
Case-21	59	M	Bacteremia Toxic shock syndrome	*S. pyogenes* (Throat culture)	-	Ceftriaxone + Vancomycin + Clindamycin	Service	7
Case-22	4	M	Mastoiditis Bacteremia	*S. pyogenes*	*S. pyogenes*	-Mastoidectomy Ceftazidime + Clindamycin	Service	14
Case-23	62	M	Mastoiditis	-	-	Ceftazidime + Vancomycin	Service	11
Case-24	4	M	Pleural empyema Bacteremia	*E. coli*	*E. coli*	Tube thoracostomy Meropenem + Teicoplanin + Amicasin	PICU	28
Case-25	93	F	Toxic shock syndrome Bacteremia		*S. pyogenes*	Meropenem + Vancomycin + Clindamycin IVIG Plasmapheresis	PICU	8 (excitus)

F: Female, M: Male.

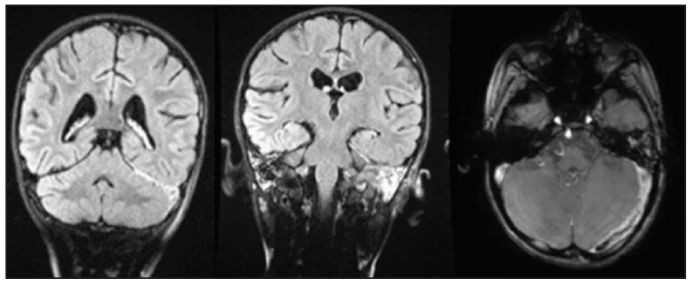

Figure 2. Radiological images of a five-year-old male patient with mastoiditis and sinus vein thrombus.

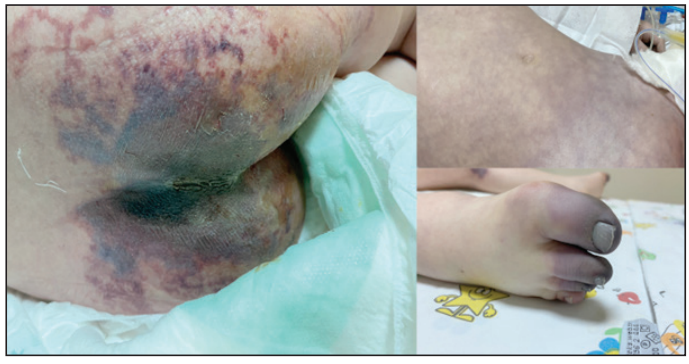

Figure 3. Photo of the lesions in an eight-year-old girl with toxic shock syndrome.

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