Medicinska istaživanja 2024; 57(2):121-126 | DOI 10.5937/medi57-47676

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

CASE REPORT

Complications of pneumococcal meningitis in a child with proteus syndrome: a case report and literature review

Slavica Ostojić[1,7], Ružica Kravljanac[1,7], Gordana Kovačević[1,7], Biljana Vučetić Tadić[1,7], Miloš Kuzmanović[2,7], Sergej Prijić[3,7], Slobodan Gazikalović[4], Aleksandra Paripović[5,7], Adrijan Sarajlija[6,7]

[1] Department of Neurology, Institute for Mother and Child Health Care of Serbia" Dr Vukan Čupić", Belgrade, Serbia

[2] Department of Hemato-oncology, Institute for Mother and Child Health Care of Serbia" Dr Vukan Čupić", Belgrade, Serbia

[3] Department of Cardiology, Institute for Mother and Child Health Care of Serbia" Dr Vukan Čupić", Belgrade, Serbia

[4] Department of Radiology, Institute for Mother and Child Health Care of Serbia" Dr Vukan Čupić", Belgrade, Serbia

[5] Department of Nephrology, Institute for Mother and Child Health Care of Serbia" Dr Vukan Čupić", Belgrade, Serbia

[6] Clinical Genetics Outpatient Clinic, Institute for Mother and Child Health Care of Serbia" Dr Vukan Čupić", Belgrade, Serbia

[7] University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Recived: 13 November 2023
Revised: 25 December 2023
Accepted: 10 April 2024

Check for updates

Funding information:
The authors did not receive specific grants from any funding agency in public, commercial, or nonprofit sectors.

Competing interests:
The authors have declared that no competing interests exist

Correspondence to:
Slavica Ostojić
Department of Neurology, Institute for Mother and Child Health Care of Serbia "Dr Vukan Čupić", 6-8, Radoja Dakića Street, 11070 Belgrade, Serbia
Email: ostojic.slavica@gmail.com

Summary

Introduction: Proteus syndrome (PS) is an exceptionally rare disorder characterized by asymmetrical overgrowth of the skin, bones, muscles, adipose and connective tissues as well as blood and lymphatic vessels.

Case presentation: We describe the clinical case of a 6.5-year-old girl with PS diagnosed and treated at the Institute for Mother and Child Health Care of Serbia "Dr Vukan Čupić". When she was 11 months old, she was treated for pneumococcal sepsis and meningitis. The disease was complicated by intracranial thromboses of venous sinuses, subdural empyema, brain infarction and a severe neurological deficit in the acute phase. Additionally, portal and mesenteric venous thromboses were identified. At 2.5 years of age, echocardiography and cardiac magnetic resonance revealed an ascending aortic aneurysm. The patient suddenly passed away when she was 6.5 years old and the cause of death has remained unknown. **Conclusion:** Despite aggressive antibiotic therapy, our patient with PS experienced multiple life-threatening complications associated with pneumococcal disease. Considering the previously documented immune disturbances in PS patients, it is plausible to speculate that our patient's immune system was compromised due to the primary diagnosis. However, as data on the immunological response in PS patients are scarce, conclusive evidence regarding the predisposition to serious infections necessitates further comprehensive studies.

Keywords: Proteus syndrome, pneumococcus, meningitis, pulmonary embolism, aortic aneurysm.

Cite this article as: Ostojić S, Kravljanac R, Kovačević G, Vučetić Tadić B, Kuzmanović M, Prijić S, Gazikalović S, Paripović A, Sarajlija A. Complications of pneumococcal meningitis in a child with proteus syndrome: a case report and literature review; Medicinska istaživanja 2024; 57(2):121-126 DOI: 10.5937/medi57-47676

INTRODUCTION

Proteus syndrome (PS) is an exceptionally rare and intricate disorder characterized by asymmetric overgrowth of various body parts (1-4). Clinical manifestations of this condition exhibit remarkable variability, with disproportional overgrowth in diverse organs and tissues, primarily the connective tissue, bone, skin, adipose tissue and central nervous system (CNS) (4). The following are also found in PS patients: hyperostosis, specific progressive cerebriform connective tissue nevi, epidermal nevi, scoliosis, other skeletal abnormalities, splenomegaly, vascular malformations, benign and malignant tumors (1-6). Notably, deep venous thrombosis with pulmonary embolism was also documented in multiple patients with PS (7,8). The mosaic expression of somatic mutation in the AKT1 gene results in random distribution of affected tissues, contributing to significant phenotypic variability among patients (9). The estimated global prevalence of PS is 1 per one million live births, with approximately 200 reported cases in the medical literature (10,11). In this report, we present the case of a Serbian child diagnosed with PS and experiencing complications related to bacterial meningitis. To the best of our knowledge, this constitutes the first genetically confirmed case of PS in Serbia.

CASE PRESENTATION

We present a case of a 6.5-year-old girl, who was initially admitted to our hospital at the age of 11 months in a comatose state. She is the third child of non-consanguineous parents who was born following an uncomplicated pregnancy, with uneventful perinatal period. Linear skin hyperpigmentation of extremities emerged when she was 6 months old. Psychomotor development remained normal in the first year of her life.

The onset of acute infection symptoms occurred the day before her admission to our hospital, marked by a fever up to 38°C, vomiting, dehydration, and somnolence. The progression of the illness included convulsions and a rapid decline in the level of consciousness from somnolence to coma, as reflected by a Glasgow Coma Scale (GCS) score of 6. Elective intubation was conducted before transferring the child to the intensive care unit, yet spontaneous respiration persisted, requiring synchronized intermittent mandatory ventilation. Throughout the initial days of treatment, the patient continued to exhibit a persistent fever, sinus tachycardia (170 bpm), hypertension (140/110 mmHg), and decreased breath sounds on the right side. There were some noteworthy phenotypic characteristics that included dolichocephaly, hyperostosis of the parietal bone, right hemihypertrophy, macrodactyly of the second finger on the left hand, and linear skin hyperpigmentation of the extremities. Upon admission, inflammation parameters were elevated, including C-reactive protein (CRP) level of 196.2 mg/L and fibrinogen concentration of 15.06 g/L. Additionally, the patient displayed anemia (hemoglobin: 80.7 g/L) and leucopenia (3.03 x 10^9/L). Findings in cerebrospinal fluid (CSF) were suggestive for bacterial meningitis: white blood cells (WBC) of 128/cubic millimeter, protein concentration of 4956 g/l, glucose concentration of 0.1 mmol/l, chloride concentration of 98 mmol/l. Streptococcus pneumoniae was isolated in blood and CSF cultures. Antibiotic therapy was immediately initiated (ceftriaxone and vancomycin). Two days later, laboratory assessments revealed signs of disseminated intravascular coagulation (DIC), including a prolonged prothrombin time (PT) of 32.1 seconds, a reduced antithrombin (AT) level of 43.1%, and a high D-dimer concentration of 8675 ng/mL. Chest radiography revealed consolidation of pulmonary parenchyma and pleural effusion. Computerized tomography (CT) of the brain on admission showed wide subarachnoid space, dilatation of the left ventricle frontal horn and thickening of the right parietal bone, while the brain parenchyma appeared normal. However, after six days, a contrast-enhanced brain CT was done due to worsening clinical condition. The scan revealed thrombosis of the sagittal sinus and cortical veins in the left parietal lobe, resulting in a hemorrhagic infarct and perifocal edema. On the eighth day of the treatment, the enlargement of the abdomen was notice, prompting suspicion of the ascites. Subsequently, a repeated ultrasound (US) examination of the abdomen revealed the presence of portal vein thrombosis and its branches, along with the observation of free abdominal fluid. The management of the thrombosis involved the administration of low molecular weight heparin, along with concurrent screening for thrombophilia. D-dimer concentration was found to be constantly elevated, while rotational thromboelastometry (ROTEM) showed extended time in INTEM with subsequent inadequate function of platelets and fibrinogen.

The patient's overall condition remained poor, marked by coma and dependence on mechanical ventilation, throughout the initial two weeks following admission. On the fifteenth day of her hospital stay it was possible to extubate the patient. A neurological assessment at this time revealed right-sided hemiparesis. The MRI examination of the endocranium on 20th day of the hospitalization indicated signs of the sagittal venous sinus recanalization, with the residual lumen narrowing, partial thrombosis of the superficial cortical sinuses in the frontal region on both sides and the parietal region on the left side. Additionally, evidence of massive cortical necrosis in the left frontal, parietal, and occipital gyri, representing sequelae of cortical infarct with hemosiderin deposits, was observed **(Figure 1B)**. Changes observed in relation to the CT scan included epidural and subdural effusions on the right (up to 3 mm) and left side (16 mm), exerting compressive effects on the left frontal lobe **(Figure 1A)**. Neurosurgical intervention was employed to drain the subdural and epidural collections. Partial

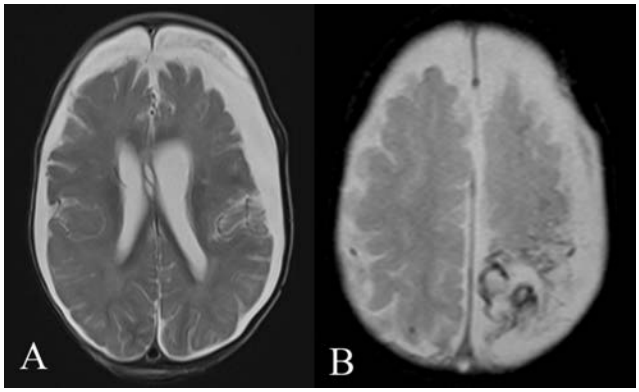

Figure 1. Axial Brain MRI T2W image shows (A) frontal epidural and subdural empyema. (B) Cortical infarction of the left frontal parietal gyrus with hemosiderin deposits.

convulsions stopped due to intravenous administration of midazolam and phenobarbital, and the treatment continued with levetiracetam, successfully achieving control of epileptic seizures. However, the resolution of meningitis was notably slow, resulting in neurological sequelae. The patient was discharged after a two-month treatment.

Regrettably, the child regressed in all acquired milestones of the early development, including sitting, standing, and walking, as well as speaking.

FOLLOW-UP AND OUTCOME

Asymmetric overgrowth was prominent in child throughout the-follow up period, with the following measurements: (1) at the age of one year, 95.2 cm (13.2 cm above +3SD); (2) at 2.5 years, 116 cm (15 cm above +3SD); (3) at 6 years, 148 cm (23 cm above +3SD), accompanied by reduced weight (20.8 kg) and BMI (9.49 kg/m2, below -3SD). The child exhibited atrophy of the adipose tissue and muscles, along with pale skin featuring linear hyperpigmentation along the neck, chest, and extremities, capillary malformation, and evident macrodactyly of the second finger on the left hand **(Figure 2)**. She had craniofacial dysmorphia characterized by an elongated face, dolichocephaly and prominent forehead. Visual impairment, severe myopia, and bilateral sensorineural hearing impairment were confirmed, necessitating the use of eyeglasses and hearing aids. Speech development remained incomplete. Neurologically, a flaccid quadriparesis, more pronounced on the right side of the body, dominated the presentation.

Full head control and the ability to sit unsupported or stand were not fully established. No epileptic seizures were recorded post-discharge, and there were no occur-

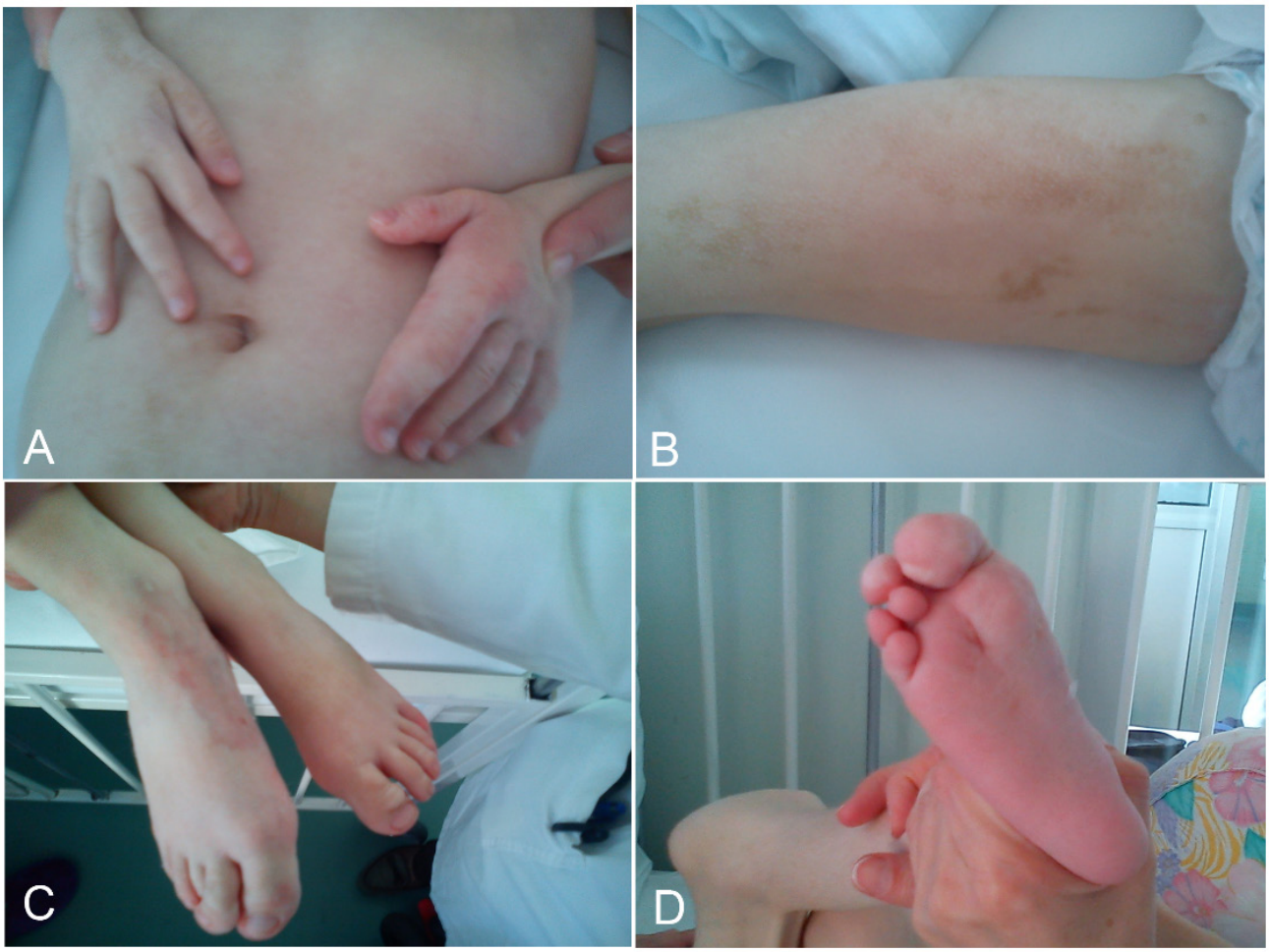

Figure 2. Phenotypic characteristics of the patient. (A) macrodactyly of the second finger on the left hand; (B) dark linear skin hyperpigmentation of the skin; (C) right hemihypertrophy and vascular skin nevus on the right leg; (D) limb hypotrophy and incipient cerebriform nevus on the plantar side of the right big toe.

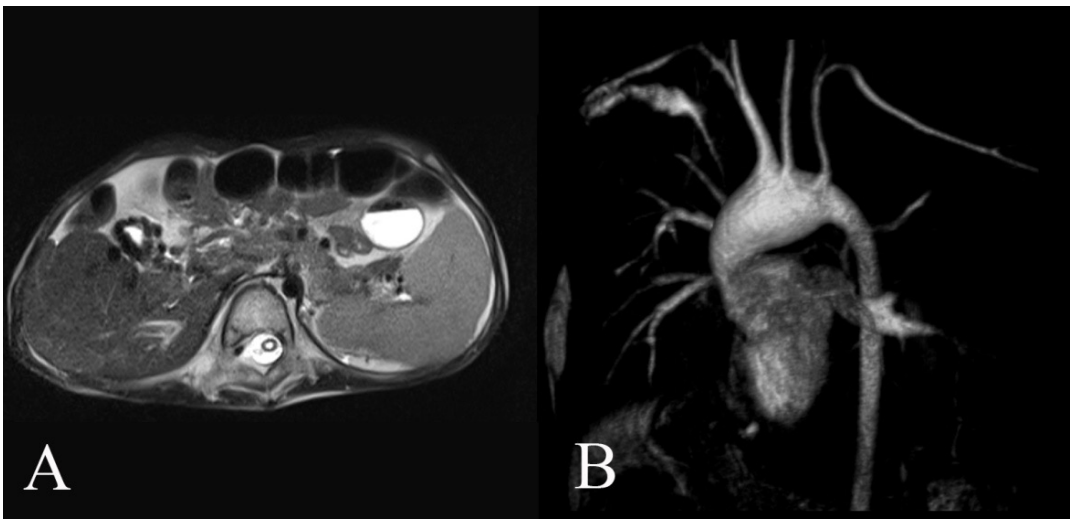

Figure 3. MRI of the abdomen and the heart. (A) Transverse T2W abdominal tomograms showing cavernous portal vein transformation and dilated portosystemic collateral blood vessels in the cholecystic lobe in the form of low IS ("flow void" structures in the blood vessels) and subsequent splenomegaly; (B) MR of the aortic arch (contrast aortography). Fusiform dilatation of the ascending aorta, aortic arch, and part of the isthmic region with a maximum diameter of 34 mm.

rences of severe infections during the follow-up period.

At the age of 2.5 years, an MR examination of the abdomen with angiography revealed splenomegaly, esophageal varicosities, and a portal vein aneurysm (Figure 3A). The examination also confirmed complete occlusion of the mesenteric artery, leading to mesenteric hypertension, and demonstrated cavernous portal vein transformation. Echocardiography and cardiac magnetic resonance disclosed an ascending aortic aneurysm (diameter up to 34 mm) and mild mitral regurgitation **(Figure 3B)**, in contrast to the normal aortic findings observed at 11 months of age. Propranolol and valsartan were prescribed to manage these cardiovascular abnormalities. A thoracic MR examination revealed fatty tissue expansion of the anterior thoracic wall, corresponding to a lipoma or a lipoblastoma. There was hyperplasia of other tissues as well. Fiber optic laryngotracheobronchoscopy indicated extreme hyperplasia of the adenoid and tonsil, with tumor tissues observed in the vocal cords and arytenoids, indicating mucosal metaplasia. Pelvic MRI confirmed the presence of large multilocular ovarian cysts measuring 49x71x41 mm and 93x63x60 mm, corresponding to multilocular cystadenomas. Elevated tumor marker levels (CA-125: 4694 U/ml) prompted gynecologists to perform bilateral adnexectomy, with histopathological findings confirming ovarian cystadenoma. In the sacral region, a surgically removed polyp was pathologically identified as an angiomatous hamartoma. The most appropriate management for suppressing growth was considered since overgrowth and the tumor masses in different tissues were impeding normal functioning of this child.

Clinical suspicion of Proteus syndrome (PS) arose when the child reached 2.5 years of age. A skin biopsy was performed, followed by the culture of fibroblasts. Samples of the DNA and the fibroblast culture from clinically affected areas were sent to the genetic laboratory at the National Institute of Health (Bethesda, USA). Here, the diagnosis of PS was confirmed at the genetic level by analyzing the samples isolated from three cell lines. A missense mutation c.49G>A (p.Glu17Lys) in the AKT1 gene, was identified as a pathologic one.

Despite regular health check-ups at our clinic, the child passed away suddenly at home at the age of 6.5. The immediate cause of death remained unknown.

DISCUSSION

Proteus syndrome (PS) is an exceptionally rare and intricate disorder characterized by malformations and abnormal overgrowth of various tissues (1-3). Affected individuals typically appear normal at birth, with abnormalities progressively manifesting during childhood. Due to the variable nature of clinical manifestations, diagnosing PS in infancy can be challenging, often resulting in initial misdiagnoses (1, 2).

In our patient with PS, meningitis caused by Streptococcus pneumoniae emerged as a severe and life-threatening complication. Initially, the child's neurological deficit was attributed solely to the severity of the infection. However, by the second year of her life, objective signs indicative of a genetically determined syndrome became apparent. Specifically, she exhibited all major and specific clinical criteria for PS, except for the presence of lung cysts (1-4). The diagnosis was genetically confirmed at the National Human Genome Research Institute in Bethesda during her third year of life.

According to the literature data, bacterial meningitis as a complication have not been reported in a patient with PS before. However, we did not prove immunodeficiency in a child with PS. There are limited publications on the immune profile of individuals with PS (12,13). The first reported case involved a 10-year-old boy with PS and mild hypogammaglobulinemia. Immunological in-

vestigations showed low serum IgG and IgA levels, along with reduced specific antibodies to pneumococcus and Haemophilus type B polysaccharides. Notably, post-immunization antibody concentrations after administering the pneumococcal vaccine in the same patient were within normal limits (12). Our patient was not immunized with the pneumococcal conjugate vaccine, as it was not mandatory in our country's immunization program at that time (2011). The patient received all other vaccines stipulated by the mandatory vaccination calendar in Serbia, including BCG, Hep B, DTaP, Hib, and IPV polio. Transitory leucopenia and lymphopenia were accounted for by sepsis. Hodge and Loungaris previously reported cases of individuals with PS exhibiting lymphopenia, which resulted in a reduction of total T and B cell counts (12,13). Notably, in contrast to our case, these patients did not experience severe infections. The role of AKT kinase appears to be significant in B cell biology, influencing apoptosis and survival, as suggested by previous research (14). Evidently, the most severe complications in our patient stemmed from a predisposition to develop deep venous thrombosis during serious bacterial infections, such as pneumococcal sepsis and meningitis. We lack evidence supporting the notion that the occurrence of thrombosis in our patient was linked to well-known prothrombotic conditions, such as factor V Leiden, prothrombin mutation in F2, deficiency of antithrombin III, protein C, or protein S. These conditions typically elevate the rate of thrombin production and fibrin clot formation. Additionally, our patient exhibited platelet dysfunction according to the ROTEM test. A similar conclusion was reached by Keppler-Noreuil *et al.*, who highlighted potential mechanisms for thromboembolism in PS, suggesting specific vascular and platelet dysfunction resulting from the AKT1 p.E17K mutation (7).

Our patient passed away at the age of 6.5 years, and the exact cause of death remains unknown as the death occurred at home, and no autopsy was performed. In addition to her predisposition to deep venous thrombosis and tumorous tissue affecting the vocal cords and thorax, compromising respiratory function, she also had an aortic aneurysm, representing a significant risk factor for fatality. This raised the question of whether an aortic aneurysm is a clinical feature of PS. In their investigation of cardiothoracic findings in PS, Mirmomen *et al.* demonstrated mild aneurysmal dilatation of the ascending aorta (with the diameter of 42–43 mm) in two out of 38 individuals (6%), with the mean age of 23 and a range of 9–61 years (15). More than half of the individuals who underwent cardiothoracic imaging of the chest exhibited pulmonary venous dilation (62%) (15). While Streptococcus pneumoniae is considered a rare cause of mycotic aneurysms (16), we can only speculate that our patient's lifespan was shortened due to, the sequelae of pneumococcal disease, to mention only one risk. Clinical studies indicate that the greatest risk of death in patients with PS occurs during childhood and adolescence (10). Early causes of death are diverse, including deep venous thromboembolism, pulmonary thromboembolism, pneumonia, respiratory failure, and others (10,17,18). Additionally, individuals with PS are at an increased risk of developing malignancies in various tissues and organs, most commonly meningiomas and gonadal tumors (15,17), as observed in our patient.

CONCLUSION

In conclusion, despite the administration of aggressive antibiotic therapy, our patient experienced multiple life-threatening complications due to pneumococcal disease. Considering the previously documented immune disturbances in patients with PS, it is plausible to speculate that the compromised immune system in our patient resulted from the primary diagnosis. However, the fact that there are scarce published data on the immunological response in PS patients, primarily due to the rarity of the disease, hinders reaching definitive conclusions about their propensity for serious infections. Further studies are essential to provide a comprehensive understanding of the immunological characteristics in PS patients.

Abbreviations:

PS - Proteus syndrome; GCS - Glasgow Coma Scale; CNS - Central Nervous System; CRP - C-reactive protein; DNA - Deoxyribonucleic Acid; ICU - Intensive Care Unit.

Acknowledgements: We express our gratitude to the Biesecker lab at the National Human Genome Research Institute at the National Institutes of Health for their molecular analysis of this patient's samples.

Conflict of interest: None to declare.

Authors' contributions: All authors have thoroughly reviewed and approved the final manuscript.

REFERENCES

1. Biesecker LG. The challenges of Proteus syndrome: Diagnosis and management. Eur J Hum Genet 2006; 14:1151–7.
2. Cohen MM Jr. Proteus Syndrome: An Update. Am J Med Genet 2005; Part C, 137C:38–52.
3. Biesecker LG, Sapp JC. Proteus Syndrome. 2012 [Updated 2023 May 25]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK99495/
4. Qaisar F, Butt NI, Ajmal Ghoauri MS, Azhar M, Javed MU, Samad A. Proteus Syndrome: A Rare Disease of Disproportionate And Asymmetric Overgrowth Of Connective Tissue. J Ayub Med Coll Abbottabad. 2023;35(1):177-9.

5. Ou M, Sun Z, Zhu P, Sun G, Dai Y. Proteus syndrome: A case report and review of the literature. Mol Clin Oncol. 2017;6(3):381-3.
6. Turner JT, Cohen Jr MM, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. Am J Med Genet 2004;130A: 111–22.
7. Keppler-Noreuil KM, Lozier JN, Sapp JC, Biesecker LG. Characterization of thrombosis in patients with Proteus syndrome. Am J Med Genet Part A. 2017;173(9):2359-65.
8. Slavotinek AM, Vacha SJ, Peters KF, Biesecker LG. Sudden death caused by pulmonary thromboembolism in Proteus syndrome. Clin Genet. 2000; 58:386–9.
9. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. New Engl J Med. 2011; 365:611– 9.
10. AlAnzi T, Al-Mashharawi E, Alhashem A. Proteus syndrome caused by novel somatic AKT1 duplication. Saudi Med J. 2021; 42:95-9.
11. Xu Y, Fu WZ, He JW, Yue H, Zhang ZL. [A clinical study of Proteus syndrome caused by a mosaic somatic mutation in AKT1 gene]. Zhonghua Nei Ke Za Zhi. 2019; 58(7):508-13. Chinese.
12. Hodge D, Misbah SA, Mueller RF, Glass EJ, Chetcuti PAJ. Proteus syndrome and immunodeficiency. Arch Dis Child 2000; 82:234-235.
13. Lougaris V, Salpietro V, Cutrupi M, et al. Proteus syndrome: evaluation of the immunological profile. Orphanet J Rare Dis. 2016; 11:3.
14. Calamito M, Juntilla MM, Thomas M, et al. Akt1 and Akt2 promote peripheral B-cell maturation and survival. Blood 2010; 115:4043-50.
15. Mirmomen SM, Arai AE, Turkbey EB, Bradley AJ, Sapp JC, Biesecker LG, Sirajuddin A. Cardiothoracic imaging findings of Proteus syndrome. Sci Rep. 2021;11(1):6577.
16. Seet C, Szyszko T, Perera R, et al. Streptococcus pneumoniae as a cause of mycotic and infected aneurysms in patients without respiratory features: Challenging diagnoses aided by 16S PCR. Ann Vasc Surg. 2019; 60:475e11-475.e17.
17. Cohen Jr MM. Causes of premature death in Proteus syndrome. Am J Med Genet 2001;101: 1–3.
18. Ferguson R, Scurr I, Ours CA, Johnston JJ, Pike K, Spentzou G. Co-occurrence of Proteus syndrome and ventricular tachycardia cardiac arrest in a teenager. Am J Med Genet A. 2023;191(5):1430-3.

KOMPLIKACIJE PNEUMOKOKNOG MENINGITISA KOD DETETA S PROTEUSOVIM SINDROMOM: PRIKAZ SLUČAJA I PREGLED LITERATURE

Slavica Ostojić[1,7], Ružica Kravljanac[1,7], Gordana Kovačević[1,7], Biljana Vučetić Tadić[1,7], Miloš Kuzmanović[2,7], Sergej Prijić[3,7], Slobodan Gazikalović[4], Aleksandra Paripović[5,7], Adrijan Sarajlija[6,7]

Sažetak

Uvod: Proteusov sindrom (PS) je veoma retko oboljenje, za koje je karakterističan asimetrični prekomerni rast kože, kostiju, mišića, masnog i vezivnog tkiva, krvnih i limfnih sudova.

Prikaz slučaja: Prikazujemo kliničku sliku devojčice uzrasta 6,5 godina sa PS, koja je dijagnostikovana i lečena u Institutu za zdravstvenu zaštitu majke i deteta Srbije. U uzrastu od 11 meseci lečena je od pneumokokne sepse i meningitisa. Bolest se komplikovala intrakranijalnim trombozama venskih sinusa, subduralnim empijemom, infarktom mozga i teškim neurološkim deficitom u akutnoj fazi. Registrovane su tromboze mezenterijalnih krvnih sudova i vene porte. U uzrastu od 2,5 godine, ehokardiografijom i magnetnom rezonancom srca otkivena je aneurizma ascendentne aorte. Pacijentkinja je iznenada preminula u uzrastu od 6,5 godina kod kuće. Uzrok smrti je bio nepoznat.

Zaključak: Uprkos primeni agresivne antibiotske terapije, naša pacijentkinje sa PS je imala brojne, po život opasne, komplikacije pneumokokne bolesti. Imajući u vidu prethodno opisane imunološke poremećaje kod pacijenata sa PS, možemo da pretpostavimo da je imunski sistem našeg pacijenta bio kompromitovan zbog osnovne bolesti. Publikovani podaci o imunološkom aspektu bolesnika sa PS su malobrojni, zbog toga što je bolest veoma retka, te su neophodna dalja istraživanja sklonosti ovih bolesnika ka teškim infekcijama.

Ključne reči: Proteus sindrom, pneumokok, meningitis, plućna embolija, aneurizma aorte

Primljen: 13.11.2023. I **Revizija:** 25.12.2023. I **Prihvaćen:** 10.04.2024.

Medicinska istaživanja 2024; 57(2):121-126