The Turkish Journal of Pediatrics 2024; 66(6): 801-808
https://doi.org/10.24953/turkjpediatr.2024.4544

Case Report

Polyarteritis nodosa with life-threatening intracranial aneurysms in a child, and treatment with infliximab

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ABSTRACT

Background. Polyarteritis nodosa (PAN) is a rare and serious form of systemic necrotizing vasculitis that predominantly affects medium and small-sized arteries, with central nervous system involvement being particularly uncommon. Treatment strategies are tailored according to the extent and severity of the disease. While conventional therapy includes glucocorticoids and conventional disease-modifying-rheumatic drugs (cDMARDs), biologic agents may be critical for severe and refractory cases.

Case. We report a case of systemic PAN in a 7-year-old girl with no prior medical history, who presented with fever, abdominal pain, and altered mental status. Initial investigations with cranial MRI and echocardiography suggested encephalitis and myocarditis, respectively. Positive SARS-CoV-2 antibodies in both cerebrospinal fluid and serum oriented the diagnosis towards multisystem inflammatory syndrome in children. Despite intensive conventional therapies with glucocorticoids, cDMARDs, and intravenous immunoglobulins, the patient's condition deteriorated. Elevated von Willebrand factor levels, hypertension, and proteinuria emerged, along with stable intracranial hemorrhage and abdominal organ infarctions on imaging, leading to the diagnosis of PAN. Cyclophosphamide was added to the treatment regimen. Three cranial aneurysms were identified on selective conventional cranial angiography. Following angiography, severe intraparenchymal bleeding was detected, leading to emergency cranial surgery. Unresponsiveness to conventional therapeutics led to treatment escalation with a tumor necrosis factor inhibitor, infliximab, resulting in clinical stabilization and allowing for successful endovascular coil embolization.

Conclusion. This case highlights the importance of considering a tumor necrosis factor inhibitor, infliximab, in severe PAN with involvement of intracranial aneurysm.

Key words: polyarteritis nodosa, PAN, infliximab, intracranial aneurysm, COVID-19.

Polyarteritis nodosa (PAN) is a rare and serious systemic necrotizing vasculitis that predominantly affects medium and small-sized arteries.[1-2] Although PAN can manifest at all age groups, its occurrence in children is particularly rare. The incidence of pediatric systemic PAN is estimated to be 0.9 to 1.8 per million.[3] The condition is characterized with a wide range of systemic symptoms that affect multiple organ systems, often resulting in complex complications. Involvement of central nervous system is relatively uncommon, nearly 2-10 % of cases.[4]

Treatment strategies are tailored according to the extent and severity of the disease. For non-severe PAN cases, the standard treatment typically involves glucocorticoids and conventional disease-modifying anti rheumatic drugs (cDMARDs) as the first-line approach.[5] In contrast, for severe and refractory cases, the use

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Received 13th Mar 2024, revised 21st May 2024, 1st Sep 2024, accepted 30th Sep 2024.

of biologic agents has shown promising results in the treatment regimen.

Multisystem inflammatory syndrome in children (MIS-C) was observed in patients exposed to SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19). MIS-C is a post-infectious inflammatory syndrome characterized by multiorgan involvement and elevated inflammatory markers. Its presentation might overlap with vasculitis, however, unlike severe vasculitis, the clinical response to the conventional therapy in MIS-C is generally favorable, and the clinical course is mostly mild and short-lasting.[6]

In this report, we present a severe case of PAN following COVID-19 infection, characterized by abdominal organ infarctions and multiple cranial aneurysms that resulted intraparenchymal hemorrhage. Remarkably, the patient's symptoms were alleviated following the initiation of a biologic agent. Our aim is to highlight the complex course and emphasize the potential role of tumor necrosing factor-α (TNF-α) inhibitor, infliximab, in treating severe systemic PAN.

Case Report

A 7-year-old girl, with no prior medical history, was referred to our pediatric emergency department with a six-day history of fever, abdominal pain, and altered mental status. On admission, the patient was pale, disoriented, confused and hypotensive. Her physical examination showed abdominal discomfort, neck stiffness, and nonpalpable purpuric rash on her palms and soles. Initial laboratory investigations revealed leukocytosis with neutrophilic predominance as 29,460 cells/μL, along with elevated acute phase reactants: C-reactive protein 438 mg/L (normal: < 5 mg/L), ferritin 778 ng/mL, procalcitonin 22 ng/mL (normal: <0.5 ng/mL), and fibrinogen 521 mg/dL (normal: 200-400 mg/dL). D-dimer levels exceeded 4400 ng/mL. Echocardiography indicated myocarditis with a reduced ejection fraction and grade 2 mitral valve regurgitation. Cranial MRI revealed widespread scattered millimetric ischemic and hemorrhagic signal changes both in the cerebral and cerebellar hemispheres, consistent with viral encephalitis. A lumbar punction deferred due to the patient's unstable condition and prolonged coagulation parameters. She was admitted to the pediatric intensive care unit with a probable diagnosis of meningoencephalitis and MIS-C. Treatment was initiated, including intravenous immunoglobulin (IVIG) at 2 g/kg, intravenous pulse methylprednisolone at 30 mg/kg/dose, enoxaparin, ceftriaxone, vancomycin, and acyclovir.

Upon achieving stabilization, follow-up cranial MRI and MRI angiography were performed, revealing an increased ischemic area size and a millimetric hemorrhagic focus in the left posterior parietal lobe. Cranial MRI angiography did not reveal any vascular abnormalities. Subsequently, a lumbar punction was performed, showing pleocytosis with lymphocytes (135 cells/mm^3, with 59% of leukocytes), elevated cerebrospinal fluid (CSF) protein levels (0.98 g/L), negative CSF cultures, and a negative meningitis PCR panel. Although the patient and her family had no recent history of COVID-19, and the patient's COVID-19 PCR test result was negative, serological tests revealed a positive SARS-CoV-2 S antibody CSF index of 34, (negative <8, positive >11), and serum levels of 9.19 COI (negative <1.0 COI, positive >1.0 COI).

Serologic tests for antinuclear antibody (ANA), antineutrophilic cytoplasmic antibody (ANCA), and anti-double-stranded DNA (anti-dsDNA) were all negative. Positive results were obtained for anti-cardiolipin IgM (14.57 PL-IgG-U/mL, normal: <12) and anti-beta-2 glycoprotein 1 IgM (44.95 U/mL, normal: <20), while C3 (0.88 g/L, normal: 0.9–1.8) and C4 (0.09 g/L, normal: 0.1–0.4) levels were just below the normal limits, and von Willebrand factor (vWF) antigen levels were elevated at 398% (normal: <160%). The levels of immunoglobulin G, A, and M before IVIG treatment were within normal limits for

the patient's age. Hepatitis B markers, including surface antigen, were negative. The patient had not previously received the COVID-19 vaccine. Serum adenosine deaminase 2 (ADA2) enzyme activity levels were within normal range and no mutations were found in the *ADA2* gene.

The patient became hypertensive, 127/98 mmHg, and developed elevated levels of proteinuria, spot urine protein/creatinine as 0.41 mg/mg, and 24-hour protein levels as 7.8 mg/m^2/hour, with normal serum creatinine, 0.32 mg/dL. Oral cyclosporine, with a dose of 2 mg/kg/day, was added to the treatment regimen to address a probable diagnosis of systemic vasculitis. The presence of elevated vWF, negative ANCA, diastolic hypertension and proteinuria raised a clinical suspicion for PAN. To confirm this diagnosis, abdominal angiography was performed to detect any aneurysmatic alterations, as aneurysms are a hallmark feature of PAN imaging studies. Abdominal computed tomography angiography revealed scattered wedge-shaped non-contrast-enhancing areas in both the kidneys and spleen, and abdominal MRI angiography showed diffusion restrictions in the intestinal walls of the proximal jejunum and ileum. A new parenchymal hemorrhage at the left posterior parietal lobe, measuring 15 x 10 mm, was observed in a follow-up cranial MRI, in addition to the previously noted abnormalities (Fig. 1). A skin biopsy for histopathological evidence was not performed during follow up.

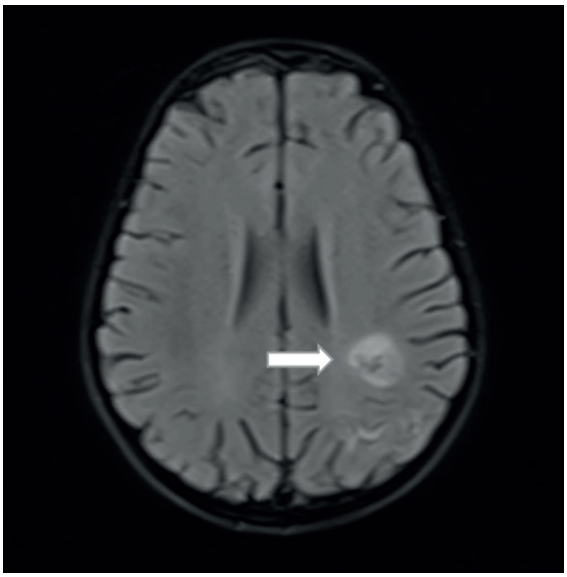

Fig. 1. Cranial magnetic resonance imaging. Axial FLAIR T2-weighted image illustrates newly developed intraparenchymal hemorrhage in the left posterior parietal lobe (arrow).

Given the progressive nature of the vasculitis despite concurrent IVIG administration (1 gr/kg for two days) and six doses of intravenous methylprednisolone (three doses on consecutive days and three doses on every other day), cyclophosphamide at a dose of 500 mg/m^2/dose was initiated, and intravenous prednisolone at 2 mg/kg/day continued. Subsequent selective conventional cranial and abdominal angiography revealed two dissecting aneurysms at the left anterior cerebral artery branches of precentral and precuneal arteries measuring 4 x 3.3 mm and 1.5 x 1 mm consequently and a bilobed dissecting aneurysm at the left medial cerebral artery (measuring 4.5 x 3.6mm, Fig. 2). No other aneurysms were shown in the mesenteric and renal arteries.

Six hours after angiography, the patient developed slurred speech and right hemiparesis. A non-enhanced brain computed tomography confirmed the presence of a large 45 x 30 mm intraparenchymal hematoma in the periventricular white matter at frontoparietal region (Fig. 3). Emergency craniotomy and intracranial hematoma drainage surgery were performed. Postoperatively, the patient was transferred to the pediatric intensive care unit, and prophylactic levetiracetam treatment was initiated. On postoperative day 1, the patient was extubated, and her right hemiplegia showed significant improvement within a week. Subsequent postoperative cranial MRI indicated regression of the intracranial hemorrhage.

Given the presence of two additional intracranial aneurysms in critical locations, a decision was made to initiate biologic therapy. Infliximab, a TNF-α inhibitor, was administered at a dose of 5 mg/kg with biweekly intervals in the first three doses, followed by a subsequent monthly regimen. Following the second infliximab dose,

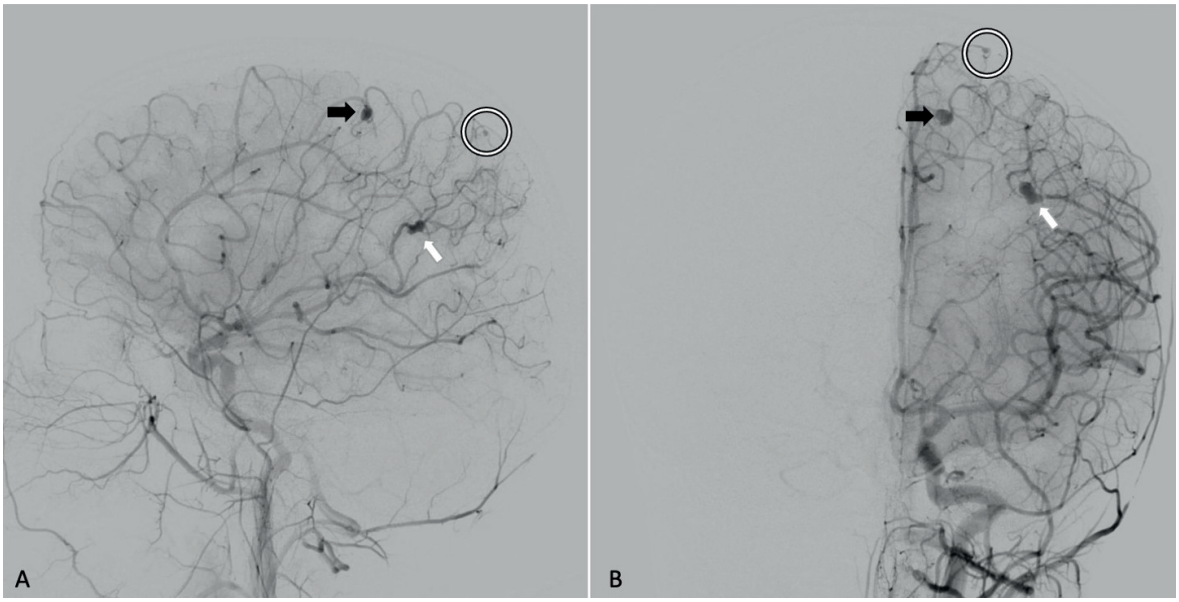

Fig. 2. Selective conventional cranial angiography (A, B). A total of three intracranial aneurysms, which are demonstrated with sagittal **(A)** and coronal **(B)** view images, two at the left anterior cerebral artery within the branches of the precuneal artery (circle), and the precentral artery (black arrow) and one at the branches of left middle cerebral artery (white arrow).

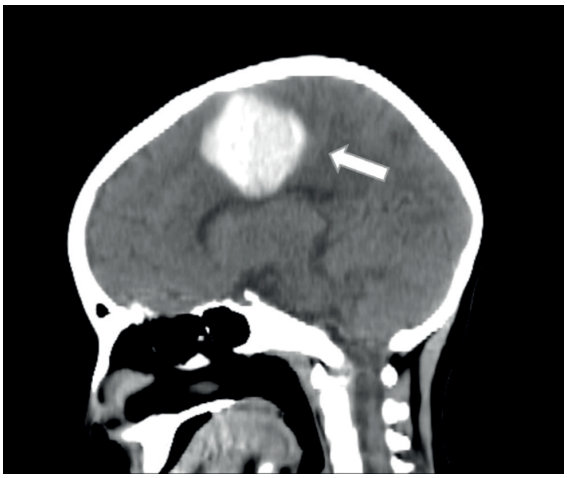

Fig. 3. Non-enhanced brain computed tomography (CT): Sagittal view of brain CT showing a parenchymal hematoma of 45x30 mm opening into the left ventricle in the left centrum semiovale region (arrow).

von Willebrand factor levels notably decreased. A second selective conventional cranial angiography was performed at another facility, and the two remaining cranial aneurysms were successfully coil embolized with no further complications.

The patient's condition remains stable after 7 months of diagnosis, biologic treatment with infliximab continues monthly, while oral prednisolone being tapered down and discontinued within two months. Parental permission for publication was obtained.

Discussion

This case is a rare and life-threatening manifestation of pediatric systemic PAN associated with COVID-19, leading to the development of intracranial aneurysms and subsequent intraparenchymal hemorrhage despite aggressive treatment with high-dose corticosteroids and cyclophosphamide. Infliximab emerged as a critical intervention, leading to clinical improvement where standard treatment failed, suggesting a potential role for biologic agents in managing severe and refractory cases of pediatric PAN cases.[7,8]

The main therapeutic options of PAN

include high-dose corticosteroids and cyclophosphamide, however, their efficacy is less certain in the presence of intracranial aneurysm, due to increased risk of rupture and hemorrhage.[9] Furthermore, significant adverse effects of these medications, such as steroid toxicity and infertility, requires a careful balance between aggressive immunosuppression and the minimalization of treatment related morbidity.[10]

In literature, Ginsberg et al.[7] reported on 26 pediatric and adult PAN patients, among whom 9 were refractory and treated with infliximab following the failure of conventional therapy. Among these 9 patients, only one, a 16-year-old boy, had a cerebral aneurysm. His condition was stabilized with infliximab treatment after four years of follow-up; however, the patient was later found to have an *ADA2* mutation. In that report, it is demonstrated that four months of infliximab is an adequate duration to assess the efficacy of infliximab response.[7] Toyoda et al.[11] highlighted the crucial part of pediatric PAN follow-up with a case of an 8-year-old who, after two years of PAN diagnosis, presented with headache and altered mental status, ultimately experiencing a ruptured superior cerebellar artery, indicating the unpredictable and severe trajectory of PAN. In literature, there are limited number of case reports on refractory systemic pediatric PAN cases with intracranial aneurysms[7,11-14], as demonstrated in Table I.

Table I. Review of pediatric refractory systemic PAN cases with intracranial aneurysm.

Reference, Year	Age / Sex	Clinical Manifestations	Angiography	Treatment	Outcome
Lee[11], 2021	7.7 / M	Fever, myalgia, arthralgia, cutaneous lesions (purpura, skin infarct)	Small microaneurysms in the distal cerebral artery branches	High dose MPS, CYC (6 doses) IFX (5 mg/kg/dose, every 2 weeks)	Remission
Toyoda[12], 2012	8 / F	New onset symptoms: Headache, LOC, right hemiparesis Known systemic PAN at the age of 6: fever, livedo reticularis, subcutaneous nodules, abdominal pain, hypertension	4 mm aneurysm in the left superior cerebellar artery	Emergency craniotomy	Remission
Ginsberg[7], 2019	16 / M	Cutaneous lesions, digital ulcers, seizures	Cerebral aneurysms	CS, CYC, MTX IFX (5 mg/kg/dose, at 0, 2, 6 weeks and every 6 weeks)	Remission
Oran[13], 1999	10 / M	Headache, fever, weakness of both arms, right sided hemiparesis	Two small aneurysms in the right anterior inferior and superior cerebellar arteries Multiple aneurysms in the branches of SMA	CYC	Remission
Sharma[14], 2010	13 / M	Seizure, LOC, facial weakness, fever, weight loss, abdominal pain	Multiple microaneurysms at the distal branches of ICA	CS, CYC	Remission

CS: corticosteroids, CYC: cyclophosphamide, ICA: internal carotid artery, IFX: infliximab, LOC: loss of conciseness, MPS: methylprednisolone, MTX: methotrexate, PAN: polyarteritis nodosa, SMA: superior mesenteric artery.

In the present case, the catastrophic presentation with high fever, altered mental status, multiorgan involvement, with myocarditis, encephalitis and cranial hemorrhage, with unresponsiveness to traditional treatment of pulse MPS and cDMARDs, suggested vasculitis over MIS-C. The elevated SARS-CoV-2 antibody levels in both CSF and serum indicate a recent COVID-19 infection as the cause of the vasculitis. To confirm the diagnosis, a selective angiography was conducted, revealing intracranial aneurysms and fulfilling the mandatory criterion of the Ankara 2008 criteria.[3] Additional criteria met include myalgia, diastolic hypertension, proteinuria and skin involvement in our case. Consequently, this report presents an exceedingly uncommon instance of PAN manifesting in conjunction with COVID-19.

The mechanism of COVID-19-related vasculitis primarily involves the downregulation of angiotensin-converting enzyme 2 by the SARS-CoV-2 virus, which subsequently results in increased levels of angiotensin II. Additionally, the interferon-1 response to the virus decreases levels of nitric oxide.[15] Both of these actions trigger vasoconstriction and endothelial dysfunction. Moreover SARS-CoV-2 triggers an inflammatory response, elevating pro-inflammatory cytokines such as IL-6, TNF-α, and activates thrombotic cascade.[15]

In the largest multicenter cohort study by Batu et al., among 41 patients with COVID-19-related vasculitis, with excluding Kawasaki disease and MIS-C, the most common type of vasculitis observed was immunoglobulin A vasculitis, followed by chilblains, post viral graft vasculitis, ANCA-associated-vasculitis, CNS vasculitis, retinal vasculitis, urticarial vasculitis, cutaneous leukocytoclastic vasculitis and acute hemorrhagic edema of infancy, respectively.[16] There were no cases of COVID-19-related PAN reported in this cohort series. This highlights the diverse nature of vasculitis associated with COVID-19. In literature, there are a limited number of adult cases reports documenting PAN occurring after COVID-19 vaccination.[17]

The differential diagnosis included consideration of the deficiency of adenosine deaminase 2 (DADA2), a rare autosomal recessive genetic disorder presenting with PAN-like vasculopathy. DADA2 leads to an autoinflammatory condition with intermittent fevers, early-onset lacunar strokes, livedoid skin rash, hepatosplenomegaly, and PAN-like vasculopathy with a positive family history.[18] The mutations in *ADA2* gene leads to DADA2 disease and TNF-α inhibitors are the first line therapy.[5,18,19] Although our patient exhibited similar symptoms, the normal ADA2 enzyme levels with absence of *ADA2* gene mutation,DADA2 diagnosis were ruled out.

The mechanism of action of infliximab, which is a monoclonal antibody, is through by blocking both soluble TNF-α and transmembrane TNF-α. Both actions reduce inflammation and modulates the immune responses. In the study by Eleftheriou et al.[20], the evaluation of biologic treatment regimens for primary systemic vasculitis of childhood revealed therapeutic responses with infliximab showed a significant decline in the median daily prednisolone doses and showed reduced vasculitis activity scores. In a narrative review evaluating PAN cases treated with biologic therapy, a total of 30 cases received infliximab.[21] Of these cases, only 3 did not achieve complete remission, and 4 experienced adverse effects, including cerebral abscess, bacterial sepsis, pertussis, and allergic reaction. Despite these side effects, infliximab's efficacy as a therapeutic option in managing resistant cases of systemic PAN patients is promising.

The multidisciplinary management approach was essential for pediatric PAN patients. Individualized step-up treatment regimens and close monitoring are crucial in optimizing for the treatment success of cases. The attempt at endovascular coiling following the stabilization of necrotizing vasculitis with infliximab provided a favorable prognosis and procedural success, as evidenced by the absence of complications post-embolization in our case.

In conclusion, this case demonstrates the complexity of managing severe pediatric PAN with multiple intracranial aneurysms. It supports the consideration of infliximab as an effective alternative option in children with refractory PAN. Additionally, this case also advocates for a reevaluation of the potential etiologies for PAN in the post-pandemic era. Further research is warranted to enhance this rare condition and refine treatment strategies.

Ethical approval

Informed consent was obtained from the legal guardians of the patient for the publication of the case report.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SAU, BS; data collection: SAU; analysis and interpretation of results: SAU, MD, BS; draft manuscript preparation: SAU, BS. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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