

Case Report

A rare case of childhood polyarteritis nodosa successfully treated with etanercept

Pragathi Kamath*, Bela Verma, Tejasi Sawant

Department of Pediatrics, Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai, Maharashtra, India

Received: 17 February 2019

Revised: 18 May 2019

Accepted: 31 May 2019

***Correspondence:**

Dr. Pragathi Kamath,

E-mail: pragathiakamath@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Childhood Polyarteritis Nodosa (CPAN) a rare and often fatal disease tends to be more common in individuals of Asian descent. Previously it was referred to as Infantile PAN. Polyarteritis Nodosa (PAN) is a systemic autoimmune vasculitis characterized by necrotizing inflammatory lesions of the medium-sized and small muscular arteries, preferentially at vessel bifurcations, resulting in formation of microaneurysms, aneurysmal ruptures with hemorrhage, thrombosis and consequently organ ischemia or infarction. It usually appears in middle or older age without gender predilection. PAN shows variety of symptoms, including general symptoms, neurological, skin, renal and gastrointestinal involvement. In particular skin lesions characterized by multiple firm waxy papules, subcutaneous nodules, livedo reticularis, ulcers and gangrene are observed in 25%-60% of patients with PAN. The etiology of systemic vasculitis is yet unknown. However, dysregulation and/or enhanced expression of pro-inflammatory substances may be involved in pathogenesis of these diseases. Tumour necrosis factor (TNF) alpha is a pro-inflammatory cytokine produced primarily by cells of macrophage-monocyte lineage which may directly participate in vascular inflammation as well as in endothelial cell death via apoptosis. In addition, TNF-alpha may play a role in neutrophil priming inducing membrane expression of Proteinase-3 or Myeloperoxidase which are subsequently recognized by ANCA-associated vasculitis (AAV). Author report a case of 14 months old male child with complaints of fever, gangrenous changes of ear lobes, tip of nose and toes, seizures, altered sensorium and hypertension. Initially Injectable Methyl Prednisolone pulse therapy was started followed by oral Prednisolone. After initiation of Etanercept treatment, his symptoms improved dramatically. Sensorium improved, skin ulcers healed faster, and gangrenous changes were arrested, fever subsided and child started accepting oral feeds.

Keywords: Childhood polyarteritis nodosa, CPAN, Etanercept PAN

INTRODUCTION

Originally described by Kussmaul and Maier in 1866 as Polyarteritis Nodosa (PAN), the term PAN was coined by Ferrari in 1903 after he recognized it as transmural inflammation.¹ PAN is a necrotizing vasculitis affecting

the small and medium-sized arteries. Vasculitis can involve the arteries in almost any organ of the body producing varied systemic symptoms and signs that may manifest simultaneously from beginning or appear sequentially over a period of months to years.² Approximately 20-50% of patient with PAN exhibit cutaneous signs. It can occur at any age, but more

commonly in fourth to sixth decade of life and males are found to be more commonly affected. The occurrence of PAN is extremely rare in childhood. Boys and girls equally affected and the mean age of presentation in 9 years.³

The causes of PAN are unknown, but the occurrence of PAN after group-A Streptococcal infection and Hepatitis-B infection suggests that it may be a post infection autoimmune response to these agents in a susceptible person. Infections with other organisms including Epstein-Barr virus, Mycobacterium tuberculosis, Cytomegalovirus, Parvovirus B 19, and Hepatitis C virus, have also been associated with PAN. There is also familial association between PAN and Familial Mediterranean fever. Pathology in PAN is necrotizing vasculitis of varying grade from mild to severe fibrinoid necrosis, thrombosis and aneurysm formation.

The clinical presentation of PAN is variable but generally reflects the distribution of inflamed vessels. Constitutional symptoms are present in most children at disease onset. Cutaneous manifestations include purpura, livedo reticularis, ulcerations, digital ischaemia and painful nodules. Arthralgias, arthritis or myalgias are frequently present. Less common symptoms include testicular pain, bone pain and vision loss as a result of retinal arteritis. The pulmonary vasculature is usually spared in PAN.

The diagnosis of PAN requires demonstration of vessel involvement on biopsy or angiography. The prognosis of untreated PAN is extremely poor, with a reported 5-year survival rate between 10 and 20%. Death usually occurs from gastrointestinal complications, particularly bowel infarcts, perforation and cardiovascular causes. Intractable hypertension often compounds dysfunction in other organ systems, such as the kidneys, heart and CNS, leading to additional late morbidity and mortality in PAN.

Early skin lesions may resemble those of Henoch-Schonlein purpura (HSP), although the findings of nodular lesions and presence of systemic features help distinguish PAN. Because pulmonary vascular involvement is very rare in PAN, pulmonary lesions suggest ANCA-associated vasculitis or Goodpasture disease.

Nonspecific laboratory findings include elevations of ESR and C Reactive Protein, anaemia, leucocytosis and hypergammaglobulinemia. Abnormal urine sediment and hematuria indicate renal disease. Elevated hepatic enzymes may suggest hepatitis B or C infection. Serologic tests for hepatitis should be performed in all patients.

Oral (1-2 mg/kg/day) and intravenous pulse (30 mg/kg/day) Prednisolone is mainstay of therapy. Oral and intravenous Cyclophosphamide are often used as

adjunctive therapy, and plasma exchanges may be warranted for life threatening disease. If Hepatitis B is identified appropriate antivirals should be initiated. Management of PAN needs multidisciplinary approach by consulting Rheumatologist, Dermatologist, Plastic surgeons, Ophthalmologists etc.

Recent studies include definitive role of biological agents in clinical improvement of Polyarteritis Nodosa. Despite aggressive medical management, 22.4% of patients die within 5 years and among the survivors, medication induced morbidity is noted.

CASE REPORT

Fourteen months old male child, first by order of birth and born of third degree consanguineous marriage, without significant past medical and family history, presented with complaints of high grade fever spikes since 2 weeks followed by gangrenous skin lesions involving bilateral ear lobes, tip of nose and toes since 10 days with history of two episodes of paroxysmal events and altered sensorium. Outside blood investigations revealed microcytic hypochromic anaemia with persistently raised total leucocytic count 25000 to 40000/mm³ with 75-90% of neutrophils with low platelets ranging from 40,000 to 90000/mm, C Reactive protein level raised to 48.6mg/dl.³ Weil Felix test was negative, coagulation studies revealed Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR) values within normal range. Renal and liver function tests with serum electrolytes were within normal range. Urine routine microscopy revealed trace proteins.

Child was on ventilatory and inotropic support for 48 hours and had received blood transfusions and platelets twice. Prior to admission at our centre, child had received low molecular weight heparin, Levetiracetam and pentoxifylline.

General examination revealed high grade fever, tachypnea with respiratory distress, tachycardia and hypertension. Child had developed dry gangrenous changes diffusely involving different parts of body including nose and cheeks, ear lobes, limbs and trunk with bilateral loss of vision. Systemic examination revealed brisk bilateral deep tendon reflexes.

Fundus examination revealed cotton wool spots suggestive of retinal vasculitis with papilledema. Blood investigations revealed Hb-8.6 g/dl, total leucocytic count- 30,200/ mm³, neutrophils-54%, lymphocytes 36% with platelet count of 86,000/ mm³. Liver and renal functions including coagulation profile repeated revealed normal studies. Viral markers HIV, HBsAg and HCV were nonreactive. Blood culture did grow any organism. Nitro Blue Tetrazolium test suggestive of activity within normal range. To rule out catastrophic APLA syndrome,

lupus anticoagulant and Ig M/Ig G anti cardiolipin antibody were sent and results were negative.

Immunoglobulin profile, IgG-1.39 gm/L, IgA-0.239gm/L, IgM-0.37gm/L, IgE-8.23 IU/ml were below normal range. Lymphocytes subset assay suggestive of normal study. C-ANCA, P ANCA were negative and ANA titer weakly positive. Pus culture grew *Pseudomonas*, sensitive to Ceftazidime. Chest X ray film had bilateral perihilar infiltrates. Computed tomogram (CT) brain showed global cerebral atrophy.

Child was started on fluids, 3% NaCl, Meropenem, Vancomycin, Metronidazole, low molecular weight heparin (LMWH), Levitracetam, Chloramphenicol and Nifedipine. Child developed new areas of gangrenous changes with extensive involvement of lower abdomen, bilateral thighs and all four extremities which progressed to ulceration with slough. Fever spikes were persistently present which were not responding to broad spectrum antibiotics.

Child was started on inj. Methylprednisolone 30 mg/kg/day one a day for 3 days and shifted to oral Prednisolone maintenance 2 mg/kg/day once a day followed by tapering. But still child had progression of lesions with ulcerative changes. Child also received Intravenous immunoglobulin 0.5 g/kg as a single dose.

Injection Etanercept was started at the dose of 0.8 mg/kg/day once a week subcutaneously. Marked clinical improvement was seen when child was on Etanercept maintenance therapy. Fever spikes subsided, gangrenous lesions were arrested and there were no new lesions.

Gradually ulcerative lesions started healing and sensorium improved. On discharge CBC was within normal limits and BP maintained on antihypertensives.



Figure 1: Extensive ulcerative rash on lower extremities with gangrenous changes of the toes.



Figure 2: Rash distributed on face, lower extremities with gangrene of toes.



Figure 3: Extensive ulcerative rash before etanercept.



Figure 4: Resolving ulcerative rash after institution of etanercept.

DISCUSSION

Polyarteritis nodosa is not common in the paediatric population with approximately only 140 cases reported in literature. Disease is limited to skin, joints and muscles in majority with a minority having nerve involvement. Constitutional symptoms are common. Most children have a chronic and relapsing benign course.

Authors patient eventually responded to Etanercept. Importantly child did not develop visceral involvement and progress to systemic Polyarteritis nodosa.

Cutaneous and systemic Polyarteritis nodosa share the same histopathological features of necrotizing arteritis of small and medium sized vessels. Kussmaul and Meier¹ described the first cases of systemic polyarteritis nodosa in 1866. Early reports confirm that cutaneous polyarteritis nodosa is a separate entity to systemic polyarteritis nodosa. Authors have limited their definition of cutaneous Polyarteritis Nodosa to disease affecting skin, muscle, joints and peripheral nervous systems with corresponding biopsy confirmation. Any evidence of visceral involvement, either clinically (central nervous system, pulmonary, cardiac, gastrointestinal or renal) or by histology (visceral biopsy) were classified as systemic Polyarteritis Nodosa. Systemic polyarteritis nodosa and cutaneous polyarteritis nodosa appear to be fairly distinct entities on a clinical continuum. There are only 5 reported cases of Cutaneous Polyarteritis Nodosa evolving into systemic Polyarteritis Nodosa.

On review of treatment regimens reported in the literature, most children respond to corticosteroids. Penicillin should be considered in children with increased ASO titers. Recent case series report success with low dose Methotrexate, Cyclophosphamide, Intravenous Immunoglobulin and biologic therapies.

Of the 25 patients reported 11 had PAN and 2 had Cutaneous Polyarteritis Nodosa as per authors case definition of skin involvement and the absence of visceral involvement. Both patients with Cutaneous Polyarteritis Nodosa responded to anti-TNF therapy one to infliximab⁴ and one to Etanercept⁵. The authors concluded biological therapy may be helpful in treating primary systemic vasculitis and recommended children with PAN who fail standard therapy or have high cumulative cyclophosphamide dose be treated with rituximab or anti TNF therapy.⁶ Eleftheriou and colleagues report the largest cohort of paediatric patients treated with biological therapy.⁷

Oral and intravenous Cyclophosphamide are often used as adjunctive therapy, and plasma exchanges may be warranted for life threatening disease. If Hepatitis B is identified appropriate antivirals should be initiated. As per clinical trials, most cases of cutaneous PAN can be treated with corticosteroids alone, Nonsteroidal anti-inflammatory agents and Methotrexate. As per recent

researches Azathioprine, Mycophenolate mofetil, Intravenous immunoglobulin (IVIg), Anti-TNF, Anti CD20 Antibodies (Rituximab), Thalidomide, Cyclosporin and have all been reported as successful treatment of refractory and cutaneous PAN.^{8,9}

To conclude, authors can state that the clinical finding and progression of PAN in childhood is highly variable and may be missed when presented with few symptoms at the beginning without definite diagnostic signs, which may appear gradually as the disease progresses. Therefore, a high suspicion and thorough clinical examination for any systemic or cutaneous finding may assist in the early diagnosis of such cases.

Authors patient was initially treated with high dose corticosteroids as standard recognized therapy for severe vasculitis. But as child had new onset of skin lesions and progressive ulcerative changes in previous skin lesions, he was given weekly regimen of Etanercept. There was marked improvement and child was discharged.

CONCLUSION

Polyarteritis nodosa is a rare systemic necrotising vasculitis of small- and medium-sized arteries that affects patients of all ages. Its incidence ranges from 2 to 9 per million in adult population. The 5-year survival rate is 13% in untreated patients and 77.6% with modern therapy. Standard treatment includes corticosteroids and cyclophosphamide. Recent studies include definitive role of biological agents in clinical improvement of polyarteritis nodosa. Early recognition and treatment of the disease are important to minimizing potential long term vascular complications. Despite aggressive medical management, 22.4% of patients die within 5 years and of the survivor's medication induced morbidity is frequent. There is great need for better treatment modalities in terms of safety and efficacy. Anti TNF-alpha, Etanercept is considered to be an effective adjuvant to steroid treatment in childhood PAN.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Kussmaul A. Über eine nicht bisher beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskelahmung einhergeht. Deutsche Arch Klin Med. 1866;1:484-518.
2. Pierce SB, Segel R, Walsh T, Barash J, Padeh S, Zlotogorski A, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Eng J Med. 2014;370(10):921-31.

3. Bansal NK, Houghton KM. Cutaneous polyarteritis nodosa in childhood: a case report and review of the literature. *Arthritis.* 2010;24;2010.
4. Bartolucci P, Ramanoelina J, Cohen P, Mahr A, Godmer P, Le Hello C, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology (Oxford).* 2002;41(10):1126-32.
5. Braun-Moscovici Y, Markovits D, Rozin A, Toledano K, Nahir AM, Balbir-Gurman A. Anti-tumor necrosis factor therapy: 6 year experience of a single center in northern Israel and possible impact of health policy on results. *Isr Med Assoc J.* 2008;10(4):277-81.
6. Brik R, Gepstein V, Shahar E, Goldsher D, Berkovitz D. Tumor necrosis factor blockade in the management of children with orphan diseases. *Clin Rheumatol.* 2007;26(10):1783-5.
7. Eleftheriou D, Dillon MJ, Tullus K, Marks SD, Pilkington CA, Roebuck DJ, et al. Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years. *Arthritis Rheumatol.* 2013;65(9):2476-85.
8. Valor L, Monteagudo I, de la Torre I, Fernández C, Montoro M, Longo M, et al. Young male patient diagnosed with cutaneous polyarteritis nodosa successfully treated with etanercept. 2014;24(4):688-9.
9. Bansal NK, Houghton KM. Cutaneous polyarteritis nodosa in childhood: a case report and review of the literature. *Arthritis.* 2010 Nov 24;2010.

Cite this article as: Kamath P, Verma B, Sawant T. A rare case of childhood polyarteritis nodosa successfully treated with etanercept. *Int J Res Med Sci* 2019;7:2837-41.