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Case Report

The "TRAPS" of Pericardial Effusion

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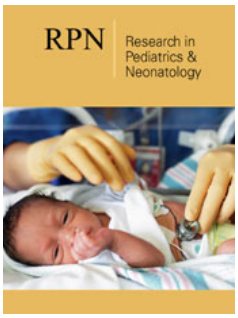

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Abstract

Background: Pericarditis is a common inflammatory condition of the pericardium, and although in the majority of cases it is due to a viral infection, autoimmune or autoinflammatory disease should be also excluded. To the best of our knowledge, our report is the first to describe a case of a child with a recurrent cardiac tamponade in whom a low penetrance gene mutation in tumour necrosis factor receptor-associated periodic syndrome (TRAPS) was confirmed.

Case presentation: A 16-year-old boy presented with symptoms of high-grade fever and worsening chest pain. The physical examination and echocardiography confirmed cardiac tamponade, requiring immediate pericardiocentesis. The clinical course, laboratory and physical findings raised the possibility of an autoinflammatory syndrome. He was treated with high doses of ibuprofen and colchicine. Eight weeks later, similar clinical symptoms developed. Remarkable clinical improvement was detected after initiation of anti-interleukin-1 (IL-1), canakinumab therapy. Genetic analysis of the tumor necrosis factor superfamily receptor 1A (TNFRSF1A) gene mutation in exon 4 revealed a heterozygous, low-penetrance R92Q variant (Arg121Gln). The diagnosis of TRAPS was based on clinical symptoms and genetic testing.

Conclusion: TRAPS has a wide range of clinical features, which make diagnosis challenging. Although pericarditis is an uncommon symptom, pericardial tamponade is even more rarely presented in patients with low penetrance variant of TRAPS.

Keywords: Cardiac tamponade; TRAPS; Anti-Interleukin-1 therapy

Abbreviations: AID: Monogenic Autoinflammatory Disease; TRAPS: Tumor Necrosis Factor Receptor-Associated Periodic Syndrome; TNF: Tumor Necrosis Factor; TNFRSF1A gene: TNF Superfamily Receptor 1A Gene; SAA: Serum Amyloid A; IL-1: Interleukin-1

Introduction

Pericarditis may occur in several infectious and non-infectious, such as autoimmune, autoinflammatory, neoplastic, and metabolic diseases. Recurrent pericarditis develops up to 15-30% of acute pericarditis. It is idiopathic in most cases, but may also be part of a monogenic autoinflammatory disease (AID) [1,2]. AIDS is a group of inherited disorders characterized by recurrent episodes of fever and systemic inflammation [3]. Pericarditis can be a symptom of many AID, such as Familial Mediterranean fever (FMF), TRAPS and hyperimmunoglobulin D syndrome. The second most common dominantly inherited AIDs is TRAPS (OMIM 142680) [4]. It is caused by the mutations in the TNFRSF1A gene on chromosome 12, which encodes the TNF receptor 1 (TNFR1) [5]. More than 160 mutations have been reported [6]. The pathogenesis of the disease still unclear. A decreased shedding of TNF-receptor leading to increased free TNF concentration was initially proposed. However, other processes may also contribute to the proinflammation, such as attenuated cell surface expression, abnormal oligomerization or misfolding with retention in the endoplasmic reticulum , decreased binding to TNF, ligand-independent signaling and reduced TNF-induced apoptosis [7,8]. The genetic heterogeneity of the disease may explain the phenotypic variability [9]. The disease usually develops during childhood and adolescence, however, about 20% of the cases may present in adulthood [10]. The disease is characterized by prolonged (1-3 weeks) recurrent episodes of fever, often accompanied by abdominal pain, myalgia, wandering maculopapular rash, and eye

inflammation. Serosal inflammation usually occurs as polyserositis [11,12]. Increased levels of acute-phase reactants are typical during fever attack [12]. The Euro fever classification requires at least one typical sign (prolonged fever/myalgia/migratory rash/periorbital oedema/contact relatives) in addition to genetic positivity, otherwise at least two clinical signs are required for the diagnosis of TRAPS [13]. The long-term complication is renal amyloidosis, which can occur in up to a 25% of patients [6]. The use of anti-TNF-α therapy is based on the path mechanism of the disease. However, it is unable to completely control systemic inflammation in 70% of patients. In refractory cases, IL-1 blockade therapy, anakinra, or the longer-acting agent, canakinumab have been used with adequate responses [14-17].

Case Presentation

A 16-year-old boy was admitted to our Intensive Care Unit with a 5-day high-grade (40 °C) fever and worsening chest pain. The family history was unremarkable. He has been hospitalized four times in the last eight months with similar symptoms. He was extremely pyrexial, tachypneic, hypotensive, tachycardic with muffled heart sounds, and required supplemental oxygen. Radial artery was palpable but weak, periorbital edema and myalgia were present. Chest X-ray showed an enlarged heart. Electrocardiogram showed upward concave ST-segment elevations in chest leads, echocardiography revealed a large pericardial effusion with signs of cardiac tamponade (Figure 1). His inflammatory markers were elevated (white blood cells: 24320/ul, absolute granulocyte number: 21640/ul, CRP: 191,5mg/l, ferritin: 440µg/l) with normal procalcitonin level. The Serum Amyloid A (SAA) concentration was markedly elevated (174.5mg/dl). Infectious (Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, human immunodeficiency virus 1-2, parvovirus B19, hepatitis -A, -B, -C, -E virus, enterovirus, Chlamydia pneumoniae, Mycoplasma pneumoniae) and autoimmune serology tests (anti-nuclear, anti-nucleosome antibody, anti-dsDNA, anti-centromere, anti-C1Q, extractable nuclear antibody, anti-saccharomyces cerevisiae antibodies, anti-neutrophil cytoplasmic antibodies, anticardiolipin, anti-beta-2-glycoprotein, anti-prothrombin) were negative. Urgent pericardiocentesis was performed and 380 opalescent pericardial fluid was drained. Microscopic examination revealed large amounts of granulocytes, culture was negative.

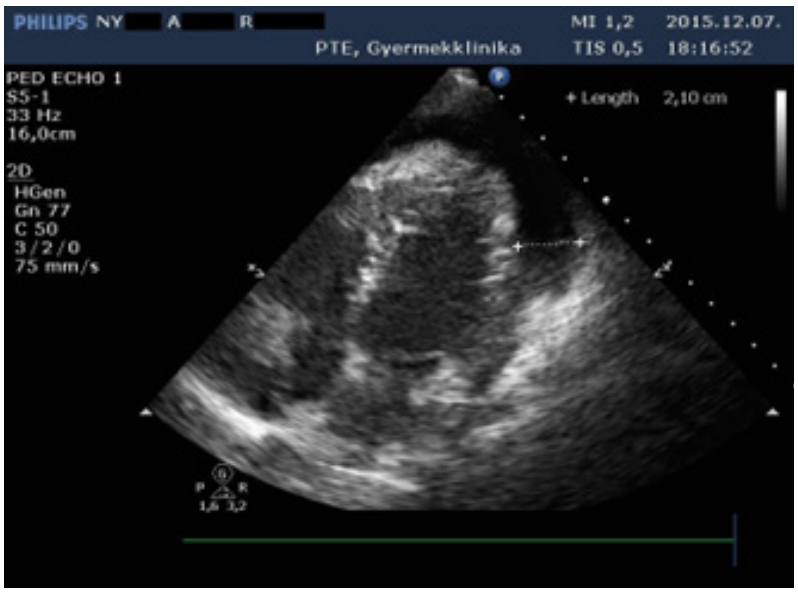

Figure 1: Pericardial tamponade.

Pathological examination ruled out malignancy, acute inflammation was reported. High dose ibuprofen, colchicine, and antibiotic treatment were started. His symptoms improved significantly, and the pericardial drain was removed after 48 hours. Laboratory parameters normalized within six days. The patient was discharged home after 10 days but continued to receive oral colchicine. Two months later he was readmitted with the same symptoms and underwent urgent pericardiocentesis. High dose aspirin (3x600 mg/day), oral steroid (2mg/kg/day) and canakinumab therapy were introduced. A dramatic reduction in acute phase reactant levels and resolution of clinical symptoms were observed. He was treated with aspirin and steroids for 3 weeks. Since the permission of the National Health Insurance Fund (NHIF) for canakinumab was comprised only for two doses, we switched to etanercept as maintenance therapy. After 20-months follow-up, the patient was persistently asymptomatic, the laboratory results returned to the normal. The treatment was well tolerated without any side effect.

The recurrent fever and serositis suggested a diagnosis of an AID. Genetic study for monogenic autoinflammatory diseases was performed. No mutations were found in the analysis of MEFV, MVK, NLRC4, NLRP1, NLRP3, NLRP12, PLC2G, PSMB8 genes. The analysis of TNFRSF1A gene revealed a heterozygous low penetrance variant R92Q (Arg121Gln) in exon 4 (Figure 2). The diagnosis of TRAPS is based on the Eurofever classification criteria.

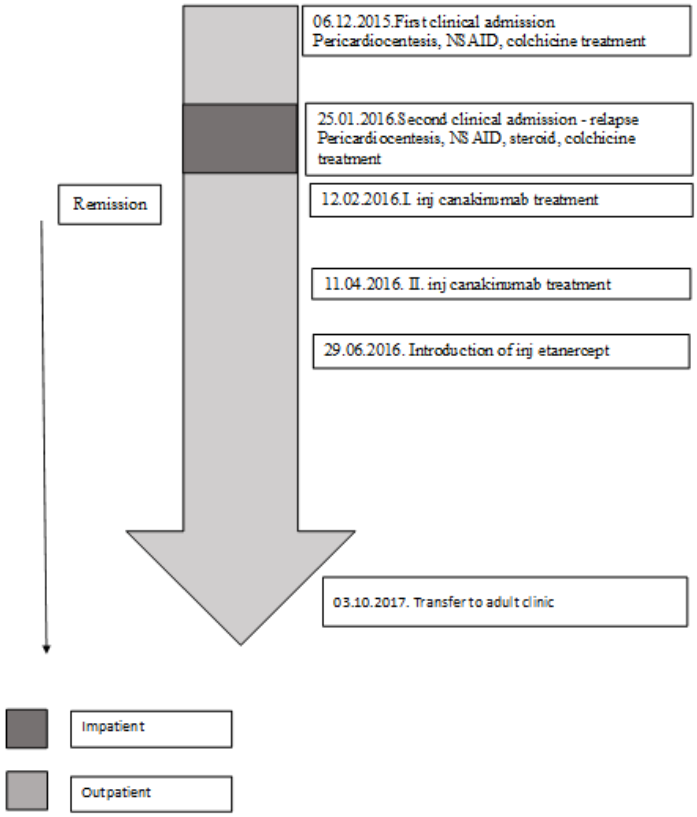

Figure 2: Timeline of care.

Discussion

This is the first report describing recurrent cardiac tamponade in childhood-onset of TRAPS. Cardiac tamponade rarely occurs in children. It is usually related to cardiac surgery, neoplasia, uremia, infection, autoimmune or AID syndromes, and 5% of cases are idiopathic. The prognosis depends on prompt recognition of the condition and management of the underlying cause. The diagnosis of AID is generally challenging. Overlapping clinical symptoms are common and genetic testing is essential for diagnosis. Based upon the TNFRSF1A gene mutation, high (cysteine) or low-penetrance (non-cysteine) variants can be distinguished in TRAPS. Variable clinical manifestation can be explained by genetic heterogeneity [18]. Cysteine mutations in TRAPS are associated with an early onset of disease, a more severe clinical phenotype and a higher risk for developing amyloidosis. It is more commonly observed in adult-onset type and positive family history of relatives with recurrent fevers is less frequent. Low-penetrance, non-cysteine mutations may cause milder, oligosymptomatic disorder. The most frequent low-penetrance variant is R92Q (rs4149584,c.362G>A; p.Arg121Gln, NP_001056.1) [19-22]. The clinical significance of this genetic variant is controversial. The frequency of this variant ranges from 1.2-5% in the general population. However, it could act as a susceptibility factor in other AID and can be observed in autoimmune disorders, too [23-27]. Idiopathic recurrent acute pericarditis has also been described in R92Q carriers [28-30].

The clinical symptoms of TRAPS are varied [31-34]. Prolonged fever is a typical symptom of the disease but chest pain occurs in only 27% of patient and less often in children [35]. Pericarditis occurs only in up to 7% of patients and is more common in adults. However, TRAPS can be diagnosed in 6% of patients with recurrent pericarditis [26-28]. Cardiac tamponade is an unusual manifestation, and only two cases were reported [36,37]. There are similarities and differences between the cases. Other clinical signs, such as pleuritis, gastrointestinal bleeding, polyartralgia and central nervous system involvements were observed in the other cases. Furthermore, due to diagnostic delay, the effective therapy started later compared to our case. A good clinical response to high dose Non-Steroidal Anti-Inflammatory Drug (NSAID) and steroid treatment, was observed in all cases, but the persistent remission could only be achieved with biological treatment.

Our patient's medical history (recurrent, prolonged high-grade fever with chest pain) and elevated inflammatory parameters raised the possibility of AID. Patients with low penetrance mutations require less steroids and immunosuppressive agents. In our patient, however, colchicine treatment was ineffective and remission was achieved with biological therapy [38].

Conclusion

Cardiac tamponade is a life-threatening condition that rarely occurs in TRAPS. Diagnosis of the underlying cause of tamponade

is essential to reduce the risk of mortality and the progression of organ damage. Genetic analysis is recommended with the medical history of recurrent fever and pericarditis towards AID.

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Ethical Approval: Was not required. The patient's parents gave a written informed consent to write this case report.

Declaration of Authorship: Bernadett Mosdósi, Zoltan Nyul and Barna Rozsai participated in the diagnosis and treatment of the patients. Gyorgy Masszi paediatrdic cardiologist, performed the scan, diagnosed the tamponade, and followed up the patient's cardiology status. Vivien Matis and Arnold Nagy organized special laboratory tests and obtained the license for biological treatment from the National Health Insurance Fund. Beata Toth performed the genetic analysis. All authors read and approved the final version of the manuscript.

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