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Infantile Periarteritis Nodosa (About 5 Cases and Review of the Literature)

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Abstract **Original Research Article**

PAN is an inflammatory and necrotizing vasculitis affecting small and medium caliber arteries of the body, rarely described in children. Its pathophysiology is complex and remains poorly elucidated, involving the deposition of circulating immune complexes in the vascular wall, neutrophil anti-cytoplasmic antibodies, the role of cytotoxic lymphocytes, cytokines, environmental factors (infections), as well as genetic susceptibility (mutations in ADA 2 and the MEFV gene). There are two main forms: a classic systemic form with visceral involvement (60% of cases) and a cutaneous form with lesions limited to the skin and muscles (30%), which usually evolve less severely. Positive diagnosis is based on the Eular/Printo/Pres criteria. The treatment depends on the form of PAN, and relies essentially on NSAIDs, colchicine, corticotherapy and immunosuppressants: azathioprine and cyclophosphamide. Our work is a retrospective study of 5 cases of PAN, collected at the IV pediatric department and the pediatric rheumatology consultation of the children's hospital of Rabat between 2009 and 2014: The diagnosis was retained on the criteria of Eular/Printo/Pres. The clinical picture was dominated by skin and joint involvement. One of our patients presented an atypical picture of PAN associated with infective endocarditis and large vessel involvement. All of our patients received corticosteroid therapy, and one of our patients benefited in addition to colchicine.

Keywords: PAN, cytokines, immunosuppressants, Eular/Printo/Pres, corticosteroid therapy.

INTRODUCTION

Periarteritis nodosa is a polysystemic necrotizing vasculitis, affecting the small and medium caliber arteries of the body. It is a rare condition in children, with an immunological mechanism, first described in 1866 by Kussmaul Maier. Although several etiological factors have been isolated, its cause remains unknown in most cases. It is important to separate primary and secondary forms, as PAN can result from infection with hepatitis B virus and sometimes other infectious agents. Although the diagnosis is evoked clinically, its confirmation relies primarily on histology with the presence of neutrophil-rich infiltration and fibrinoid necrosis of the arterial vessel wall, and/or on imaging by the demonstration of small arterial aneurysms. Our work consists in bringing our contribution from the study of 5 observations of patients with PAN, collected in the pediatric service IV and in the consultation of pediatric rheumatology at the Children's Hospital of Rabat.

METHODS AND RESULTS

Our work is a retrospective descriptive study conducted in the Pediatric IV Service of the Children's Hospital of Rabat (HER). Our study focused on 5 patients, hospitalized our training whose follow-up was maintained within the same unit since the diagnosis of pathology was made.

We report the observation of 5 patients (1 boy / 4 girls) with a sex ratio = 0.2. The average age at diagnosis was 7.5 years (3.5_12 years). The onset was abrupt in 1 patient, and the general signs were dominated by alteration of the general state. A hypertension of 15/10 was noted in one patient. The cutaneous manifestations were dominated by subcutaneous dermal-hypodermal nodules Livedo reticularis for 3 patients, purpuric lesions for 3 patients and 2 patients presented a cutaneous cyanosis of the tongue, 3 patients presented a necrosis of the extremities with necrotic ulcerations. Arthralgia was found in all 5 patients. Myalgia in 2 patients, bilateral optic neuropathy with retinal hematoma in one patient,

vasculitis of a branch of the temporal artery at the level of the OG. An inflammatory syndrome was found in all patients. The search for NAA and anti-DNA CA was performed in all our patients, in the fear of a systemic disease notably SLE. In one case, NAA was positive at 1/80. ANCA tests were performed in all patients and were always negative. The determination of C3, C4 complements concerned 3 of our patients, it came back normal. One of our patients presented a renal failure (urea=2g/l; creatinine=35,2 mg/l) with a nephrotic syndrome, the echodoppler of the lower limbs was normal.The skin biopsy was made in all the patients returned in favor aspect of vasculitis in favor of periarteritis nodosa (fibrinoid necrosis of the wall, inflammatory infiltrate mononucleate). In our series, no case of hepatic B virus infection was detected. Indeed, all our patients were tested for HBsAg which was negative in all cases. One patient presented a positive covid19 serology IgM positive = 2.09, IgG negative = 0.15.A Heart-Echo was performed in all our patients. One of our patients presented appended vegetation of the mitral valve that is rheumatic with a grade 3 mitral leak. In our PAN series, all of our patients had angiographic exploration. It was normal in two cases, and revealed the presence of renal artery aneurysms in one case, a partially thrombosed subrenal abdominal aorta aneurysm up to the bifurcation of the iliac arteries, and a splenic artery aneurysm with splenic infarction in the other case. In our series, corticosteroid therapy was administered to all patients. Two cases received exclusively oral corticosteroids; prednisone was administered at a rate of 1.5 to 2 mg/Kg/d. The other 3 patients received oral and bolus corticosteroids; the dose of methylprednisolone corresponded to 1g/1.73m2 of SC/bolus. All our patients undergoing corticosteroid therapy benefited from adjuvant treatment. In our study, no patient was put on NSAIDs. Indeed, the 3 reported skin cases were admitted with signs of severity (necrosis of the extremities and necrotic ulcerations).

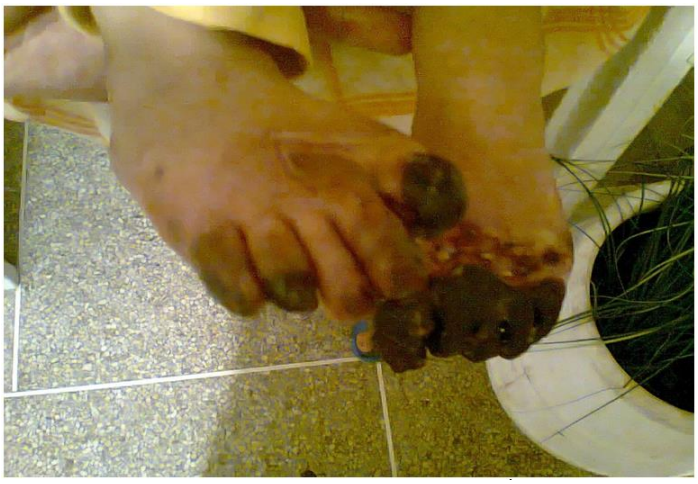

IMAGE1: Photo of the patient's feet showing bilateral toe necrosis with distal metatarsal involvement

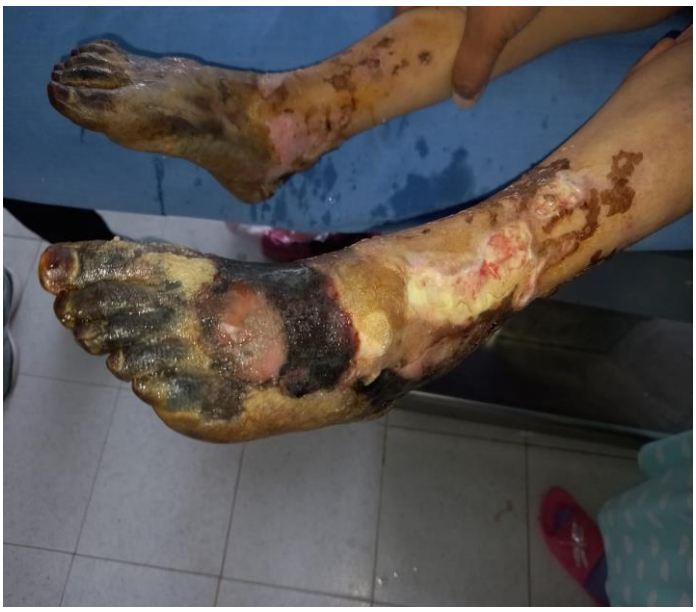

IMAGE2: Photo of the feet of the second patient showing bilateral necrosis of the toes

DISCUSSION

Periarteritis nodosa is a rare disease. The incidence and prevalence are not well known in the pediatric population. The largest series come from Turkey, India, Italy, and Great Britain. Reimold estimates that fewer than 150 cases of PAN in children were reported until 1976, but it is likely that many cases were not diagnosed or published [1]. Dillon reported 36 cases in 1993 at Sick Children Hospital in London [2]. Ozen reports 31 cases from 1979 to 1991 at the Ankara Hospital [3, 4]. 69 children who met the current classification criteria of PAN (EULAR/PRINTO/PRES criteria) were identified over a 32-year period from January 1980 to January 2012 [5]. NAP affects all populations and all ages. In adults, it predominates between 40 and 60 years of age, the average age of diagnosis is 51 years with a slight male predominance [6]. In the 2004 Ozen pediatric survey, the mean age was 9.05+- 3.57 (extremes 1-16 years), with no gender predominance [4]. In the Falcini pediatric cohort in 2014, the mean age of onset was 7.9 years (from Extremes 2- 16 years), the mean age at diagnosis was 8.9 years (from Extremes 3.6-16.2) and the sex ratio was 1.4 [7]. The clinical picture is usually noisy, with a rapid onset over a few days. Fever is in the foreground, almost constant, high, sometimes poorly tolerated, associated with a general condition (AEG): asthenia, anorexia, sometimes weight loss. Sometimes, even in the absence of general and systemic signs, the onset can be severe, as was the case in 2 cases of PAN revealed by digital necrosis [8], and in another observation that presented a necrosis of the tongue as the first manifestation of the disease [9]. Cutaneous manifestations: are present in the majority of patients, sometimes with an onset delayed by a few days in relation to the fever. They are mainly subcutaneous, bluish, painful knots, localized to the extension sides of the legs and forearms[8]. Myalgias are secondary to muscle ischemia. They are frequent (more than 2 out of 3 cases), often intense, resistant to analgesics, and sometimes incapacitating, leaving the patient bedridden. They are diffuse or localized, spontaneous or triggered by pressure.

Joint pain is frequent, affecting mainly the large joints, knees, ankles, elbows and wrists. Arthralgias usually do not affect the shoulders or hips, the limbs are respected [8, 10]. True arthritis is much rarer and is seldom in the limelight. All these symptoms will regress with treatment, often slowly [8]. Peripheral vascular manifestations: are represented by gangrene, hematomas, Raynaud's phenomenon, necrosis of the tongue. In our series, 3 cases of necrosis and cyanosis of the extremities with an evolution towards gangrene were reported leading to amputation. Renal manifestations: As far as renal involvement is concerned, we distinguish two forms according to the type of renal involvement: classic systemic PAN and microscopic PAN or PAM.

Renal involvement is a serious complication of NAP, as it is one of the main causes of death. It is clinically manifested by declining edema, usually minimal proteinuria, hematuria, rapid onset of renal failure, most often oligoanuria, and hypertension, often with malignant progression [4, 8]. The inflammatory syndrome is an important element to orient the diagnosis but does not confirm it given its lack of specificity. There is little or no biological evidence of autoimmunity in pediatric PAN [8].

Significant levels of rheumatoid factor, antinuclear antibodies, or anti-DNA antibodies are detected in 10% to 20% of cases of childhood PAN. They are of no particular significance, but may help to rule out other differential diagnoses at the outset (systemic lupus erythematosus (SLE), a juvenile idiopathic arthritis) [8]. The serum complement study does not provide relevant information, as levels may be normal, low or high. It is performed when there is a diagnostic hesitation between PAN and SLE [8]. In adults, PAN is classically associated with hepatitis B, but this association is less frequent in children. Analysis of circulating immune complexes has shown in some cases that the antigen may be a component of hepatitis B virus [16].

Radiological explorations have a double interest: to confirm the diagnosis, to make the lesion assessment of the affected organs. The frequency of myocardial damage, often asymptomatic, justifies the systematic performance of this examination. It may reveal more marked abnormalities: cardiomegaly, decrease in systolic ejection fraction, valvular insufficiency, pericardial effusion [21]. As NAP is a pathology known to be a source of aneurysms and thrombosis, an echo-Doppler examination is necessary as soon as the diagnosis is suspected. Angiography allows the diagnosis to be made by showing specific and/or suggestive signs. Thus, the demonstration of microaneurysms and stenosis of medium caliber arteries are usual characteristics of PAN. Another interest of angiography is the evaluation of the prognosis in particular by revealing renal and digestive involvement. It is also an objective means of monitoring after treatment [20]. The demonstration of microaneurysms on small and medium caliber arteries of the kidney, liver or any other viscera is very suggestive of the disease. These microaneurysms are often multiple (10 or more per affected organ), measuring between 1 and 5 mm. They can sometimes reach several centimeters with an increased risk of rupture and would be at the origin of perirenal or retroperitoneal hematoma. Usually large vessel involvement is not part of the clinical picture of PAN, there are only a few cases published in the literature concerning neck vessel involvement [22].

Skin and/or muscle biopsy is one of the two examinations, together with angiographic explorations, that allow the diagnosis of PAN to be made with

certainty [21]. The histological diagnosis can be made on biopsy of any affected organ (testis, nothing). The skin biopsy should be deep, involving the hypodermis, and performed on an area of infiltrated purpura or a subcutaneous nodule. In case of ulceration, it is preferable to biopsy near the center of the ulceration rather than in the periphery. It should be performed as soon as suspicious lesions appear, as lesions are often transient, especially subcutaneous nodules. A late biopsy may be negative or may show only nonspecific vasculitis images [21]. Histological examination shows lesions of different ages that coexist with intact vessels. Typically, characteristic images of necrotizing panarteritis of medium- and small-caliber arteries with full-thickness fibrinoid necrosis of the wall are demonstrated. Most of these lesions are segmental and focal, with a preferential localization at the arterial bifurcations. The presence of aneurysms is highly specific for PAN [21]. In the initial stage, there is thickening of the vessel walls, particularly the intima and media, with edema, fibrinoid necrosis predominating in the medial part of the media with sometimes destruction of the internal elastic boundary (best seen on orcein staining). An inflammatory infiltrate with a majority of neutrophils and some eosinophils and lymphocytes is associated. Leukocytoclasia may be observed. Inflammation is mainly arteriolar but may extend slightly into the adjacent adipose panniculus or deep dermis with an inflammatory infiltrate that is mainly lymphocytic. Direct immunofluorescence studies have been performed on PAN lesions. They show the presence of deposits composed of Ig M (excluding IgG and IgA), C3 and fibrin, located in the vessels of the deep or superficial dermis or both. Skin biopsy was performed in all patients. The results were in favor of a typical histological appearance of PAN. It was a leukocytoclastic vasculitis with fibrinoid necrosis, which confirmed the diagnosis.

PAN is an inflammatory vasculitis with multivisceral localization and a potentially serious prognosis in the absence of prompt management. A wide range of therapies is now available, and the prognosis has been significantly improved by the introduction of corticosteroids and immunosuppressants. Any prescription must take into consideration the balance between the benefits and risks involved. Classically the treatment will obey the usual therapeutic escalation from the best tolerated and most effective drug to the most aggressive treatments. The molecules most used in pediatrics are the following: acetylsalicylic acid (ASA), ibuprofen, diclofenac and indomethacin (which has no MA in pediatrics before 15 years of age. however extremely effective in older children > 12 years, its prescription is tolerated). NSAIDs are indicated for cutaneous forms of NAP. They should be used as a first-line treatment, provided that there are no signs of severity, such as ulceration or skin necrosis. However, in approximately the majority of cases, NSAIDs are insufficient to control the disease, requiring the use of corticosteroids [21].

In our study, no patient was put on NSAIDs. Indeed, the 3 reported skin cases were admitted with signs of severity (necrosis of the extremities and necrotic ulcerations).Corticosteroid therapy occupies a central place in the treatment of PAN in children. It is the first treatment proposed with effectiveness in NAP. It remains the most widely used therapy according to most authors [5]. Two modes of administration are possible: oral or intravenous bolus. Treatment of the systemic form is based primarily on oral corticosteroid therapy, at a high dosage for the initial treatment, in the order of 1 to 2 mg/kg/day, and may be preceded by 3 intravenous boluses of methylprednisolone, at a dose of 30 mg/kg/day, which have a spectacular effect on the general signs. The duration of the initial treatment depends on the clinical response, but generally lasts several weeks until the disease is under control and clinical abnormalities disappear. After a phase of rapid dose reduction, the decrease must be cautious and progressive with the aim of reaching a mid-dose after 3 months of treatment. This dose reduction should be interrupted in case of a new disease flare [12].

In case of resistance to oral treatment, threatening visceral damage (pericarditis, pleurisy, nephropathy) or severe disease, CPM or azathioprine should be combined with venous corticosteroid therapy [3]. In our series, 2 observations of systemic PAN were reported: -the first case benefited from 3 boluses of methylprednisolone 3 days in a row with oral relay at a dose of 1mg/kg/day then progressive degression to the minimal effective dose with adjuvant treatment.

The other case benefited from a corticosteroid therapy (prednisone) per os at a dose of 2mg/kg/day for 2 months and then progressive degression to the minimal effective dose associated with an adjuvant treatment.

The treatment of the cutaneous form is not codified and is adapted according to the severity of the disease and its evolution. In fact, various treatments are reported in the literature concerning the treatment of this form colchicine, dapsone, NSAIDs, corticosteroids and/or immunosuppressants, IGIV but there are no controlled studies allowing to appreciate their real efficiency [30]. In our study, 3 cases of cutaneous NAP were reported: the first case was treated with oral corticosteroids with adjuvant therapy associated with colchicine and anticoagulant therapy, but this did not prevent the appearance of distal gangrene in the two fingers of the right hand, which led to their amputation. The other two cases received 3 boluses of methylprednisolone (due to necrosis of the extremities) followed by prednisone-based oral corticosteroid therapy at a rate of 1 mg/kg/day with adjuvant treatment.

CONCLUSION

Periarteritis nodosa is an inflammatory and necrotizing systemic vasculitis rarely described in children, of immunological origin, the pathophysiological mechanisms of which remain poorly understood. Its treatment involves corticosteroid therapy and, for severe forms, cyclophosphamide infusions. Secondary forms of PAN have become the most frequent, including those associated with hepatitis B virus, other infectious agents and haemopathies. The prognostic factors are gastrointestinal involvement, renal failure, cardiac manifestations and central nervous system involvement. Uncontrolled vasculitis and infections, as well as renal, gastrointestinal and cardiovascular manifestations are among the causes of death.

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