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Streptococcal tonsillitis related reactive arthritis – clinical, ultrasound imaging and immunohistochemical study

ANCA-EMANUELA MUŞETESCU[1)], MARIUS FLOREA[2)], MIRCEA-CĂTĂLIN FORŢOFOIU[3)], ANA-MARIA BUMBEA[4)], ANDREEA DANIELA TUDORANCEA[2)], CRISTINA CRIVEANU[1)], CRISTINA-ELENA GOFIŢĂ[2)], PAULINA-LUCIA CIUREA[1)], ALEXANDRU ŞTEFĂNESCU[5)], ŞTEFAN-CRISTIAN DINESCU[2)], CARMEN AURELIA MOGOANTĂ[6)]

[1)]*Department of Rheumatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*PhD Student, Department of Rheumatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

[3)]*Department of Internal Medicine, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

[4)]*Department of Medical Rehabilitation, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

[5)]*PhD Student, Department of Pathology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

[6)]*Department of Otorhinolaryngology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

In clinical practice and literature studies, the most common condition associated to streptococcal tonsillitis used to be acute rheumatic fever (ARF). Several publications in the late years report a more frequent and distinctive entity from ARF following *β*-hemolytic group A streptococcus infection in patients with post-infectious arthritis, that do not fulfill the modified Jones criteria, the so-called post-streptococcal reactive arthritis (PSRA). A distinctive pattern of clinical framing and biological profile in patients with PSRA following streptococcal tonsillitis is described, with a non-migratory, additive, recent onset (7–10 days) arthritis that affects small and large joints as well, with a bimodal peak of incidence at 8–14 and 21–37 years of age, with variate response to non-steroidal anti-inflammatory drugs and has a tendency for recurrence and persistence. Sacroiliitis, although rare, is described in human leukocyte antigen (HLA)-B27 positive PSRA patients. The main objective of the current study was to evaluate various immunohistochemical patterns of streptococcal tonsillitis in patients with PSRA and find possible correlations with the clinical, biological and ultrasound profile.

Keywords: streptococcal infections, tonsillitis, arthritis, ultrasonography, immunohistochemistry.

Introduction

In clinical practice and literature studies, the most common condition associated to streptococcal tonsillitis used to be acute rheumatic fever (ARF) [1]. According to 1992 Jones revised criteria, ARF diagnosis is set in the presence of two major manifestations that include polyarthritis, carditis, chorea, erythema marginatum and subcutaneous nodules or one major and two minor criteria including arthralgia, fever, high acute phase reactants and a prolonged PR interval on the electrocardiogram (ECG) [2]. Several publications in the late years report a more frequent and distinctive entity from ARF following *β*-hemolytic group A streptococcus (GAS) infection in patients with post-infectious arthritis that do not fulfill the modified Jones criteria, the so-called post-streptococcal reactive arthritis (PSRA) [3].

A distinctive pattern of clinical framing and biological profile in patients with PSRA following streptococcal tonsillitis is described, with a non-migratory, additive, recent onset (7–10 days) arthritis that affects small and large joints as well, with a bimodal peak of incidence at 8–14 and 21–37 years of age, with variate response to non-steroidal anti-inflammatory drugs (NSAIDs) with a tendency for recurrence and persistence [4]. Sacroiliitis, although rare, is described in human leukocyte antigen (HLA)-B27 positive PSRA patients [5, 6]. HLA-B27 genetic background is frequently positive in most common infections associated with reactive arthritis of enterogenic or urogenital determinism, such as *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia* and *Chlamydia trachomatis* [7]. From the first description of post-streptococcal arthritis, in 1959 [8] to the current days, a heterogeneous variety of symptoms and signs were related to PSRA and while attempts to crystallize a set of diagnostic criteria were done by Ayoub & Ahmed [9] and Barash *et al.* [10], failure in validating a distinctive set occurred subsequently making diagnosis, interpretation and treatment strategy quite difficult.

Proof of prior GAS infection is mandatory though, through microbiological assays – throat cultures or rapid antigen detection test (RADT) or by serological confirmation of recent infection using anti-streptolysin O (ASLO) and anti-deoxyribonuclease B (anti-DNase B) antibodies titer [11].

The complex attitude regarding diagnosis and therapeutic approach in adult patients with musculoskeletal symptoms after a GAS – proven tonsillitis offered an important research path as the main objective of the current study was to evaluate various immunohistochemical (IHC) patterns of streptococcal tonsillitis in patients with PSRA

and find possible correlations with the clinical, biological and ultrasound profile.

Patients, Materials and Methods

The study group consisted of 17 patients, 10 male patients and seven female patients, aged between 19 and 37 years. All the patients had a history of tonsillitis, either of recent onset or a chronic form with recurrent flares. Also, all patients reported the occurrence of an arthritis episode within a one-month interval after the last tonsillitis flare. No patient had any history of reactive arthritis (ReA), inflammatory bowel disease or any other form of seronegative spondyloarthropathy. Other causes of arthritis, such as rheumatoid arthritis, septic arthritis, crystal deposition disease, connective tissue disease were excluded.

We established three mandatory features needed for inclusion in the study, *i.e.*, tonsillitis, evidence of streptococcal infection and non-migratory arthritis. Tonsillitis was confirmed in the setting of clinical features, such as sore throat, hyperemia on the anterior pillars, tonsillar hypertrophy, crypt debris and intratonsillar or peritonsillar abscesses. Positive serology profile for GAS infection included high ASLO (>200 IU/mL) and anti-DNase B (>188 IU/mL) antibody titer. Additional microbiological tests consisted of throat cultures or RADT. Each patient had proof of GAS infection through at least one of the aforementioned methods. Additional laboratory tests consisted of erythrocyte sedimentation rate (ESR) with normal value <15 mm/1 h, C-reactive protein (CRP) with normal value <5 mg/L, rheumatoid factor (RF) with normal value <14 UI/mL, antinuclear antibodies (ANA) and complement C3 with normal range 90–180 mg/dL. Cardiac involvement secondary to GAS infection was evaluated through an ECG and echocardiogram.

Arthritis affected both small and large joints and was characterized as monoarthritis, oligoarthritis (two to four joints) or polyarthritis (five or more joints). Plain radiography of the sacroiliac joints, knees and ankles were performed. A more in detailed analysis of joint inflammation was made through musculoskeletal ultrasonography (US), having the benefit of detecting subclinical synovitis and also allowing a more accurate US-guided arthrocentesis. Examinations were done on a MyLab25™Gold US system, using a multifrequency probe of 6–18 MHz. We systematically examined both knee and ankle joints and also other sites with clinically significant arthritis, probing for synovial thickening, joint effusion or both. Synovial fluid extracted from the sites of joint effusion was then sent for further cytological and bacteriological analysis.

Of the 17 patients included in the study, 13 had a history of chronic tonsillitis and were scheduled for tonsillectomy. Tissue specimens were fixed in paraffin blocks and then seriate sectioned were obtained. Slides were stained with Hematoxylin–Eosin (HE) to reveal histological features of the tonsil tissue and pathological changes associated with various grades of inflammation. IHC study was performed using the following antibodies: CD20 for B-lymphocytes, CD3 for T-lymphocytes and CD68 for macrophages. After microscopy analysis, images were captured using a microscope C-mount camera and stored in digital format.

Results

Our study group consisted of 17 patients with mean age of 27 years (±5.26), with a relative even male to female ratio (10:7). All patients reported a recent episode of sore throat prior to the onset of articular symptoms, with a mean interval of 10 days (ranging from 4 to 17 days). In order to correctly classify the patients as having PSRA, it was mandatory that they do not fulfill the Jones criteria for ARF [2]. Through ECG and echocardiogram, carditis and valvular disease could be ruled out. Also, chorea, erythema marginatum and subcutaneous nodules were absent in all cases.

Evidence of GAS infection was confirmed in all patients through at least one of the various serological and bacteriological methods. The most positive results were obtained by the anti-DNase B antibody test in 88% of the patients followed by ASLO, GAS throat cultures and RADT with 82%, 82% and 76%, respectively. Peripheral leukocytosis was present in eight (47%) patients; also, high levels of inflammation markers ESR and CRP were seen in the majority of cases. There was no positive result for RF and ANA and also C3 levels were within normal range in all patients. Laboratory characteristics of patients are featured in Table 1.

Table 1 – ***Study group clinical, laboratory and US features***

No. of patients	17
Mean age [years]:	27
▪ range	19–37
Male to female ratio	10:7
Interval between tonsilitis and arthritis [days]:	
▪ mean	10
▪ range	4–17
Evidence of GAS infection [%]:	
▪ ASLO	82
▪ anti-DNase B antibodies	88
▪ throat cultures	82
▪ RADT	76
Arthritis pattern, *n* (%):	
▪ monoarticular	3 (18)
▪ oligoarticular	6 (35)
▪ polyarticular	8 (47)
US confirmed synovitis and/or joint effusion, *n* (%):	
▪ mild	8 (47)
▪ moderate–severe	6 (35)

US: Ultrasonography; GAS: *β*-Hemolytic group A streptococcus; ASLO: Anti-streptolysin O antibodies; DNase B: Deoxyribonuclease B; RADT: Rapid antigen detection test.

Clinical pattern of arthritis (see Table 1) varied from patient to patient, with most prevalent being the polyarticular involvement in 47% of the cases (eight patients), followed by oligoarticular and monoarticular in 35% and 18% of cases, respectively. Both small joint and large joint involvement was observed, with the latter being more prevalent. Most (94%) patients featured arthritis pattern in the lower limbs, particularly in the knees and ankles. Three (17%) patients reported symptoms in both lower

limbs and upper limbs (elbows or wrists), while just one patient had only upper limb articular involvement. Only one patient featured suggestive signs of sacroiliitis on radiology examination. Signs of enthesitis were present in four patients, two of them with patellar tendon involvement and the other two at the Achilles tendon.

US evaluation provided additional information about the degree of inflammation in joints with clinical signs of arthritis and could also reveal sub-clinical sites of inflammation. The majority (82%) of patients showed signs of synovitis and/or joint effusion in at least one of the examined sites (Figures 1 and 2a), some of them showing also signs of tenosynovitis (Figure 2b). The US findings were labeled as mild in eight (47%) patients and moderate–severe in six (35%) patients. Arthrocentesis performed at the sites of inflammation with sufficient joint effusion revealed high values of white blood cells (*i.e.*, >10 000 cells/mm^3) in 76% of cases, all of which had a predominant neutrophil subpopulation.

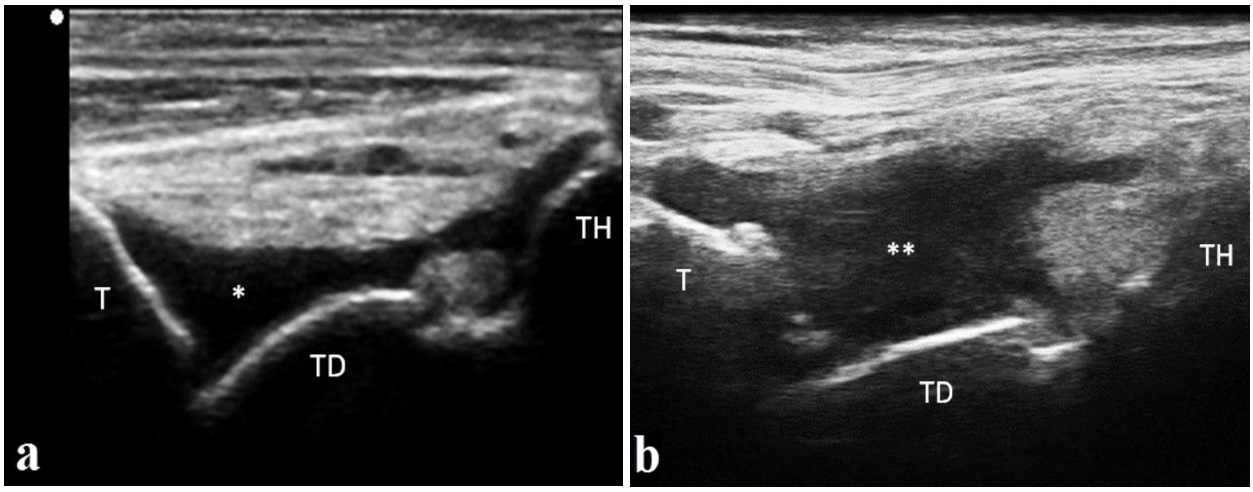

Figure 1 – ***US image in longitudinal section of the ankle joint recess:(a) Grade 2 effusion of the anterior recess of the tibio-talar joint (asterisk); (b) Hypoechoic mass at the anterior recess of the tibio-talar joint corresponding to a grade 3 synovial proliferation (double asterisk). T: Tibia; TD: Talar dome; TH: Talar head.***

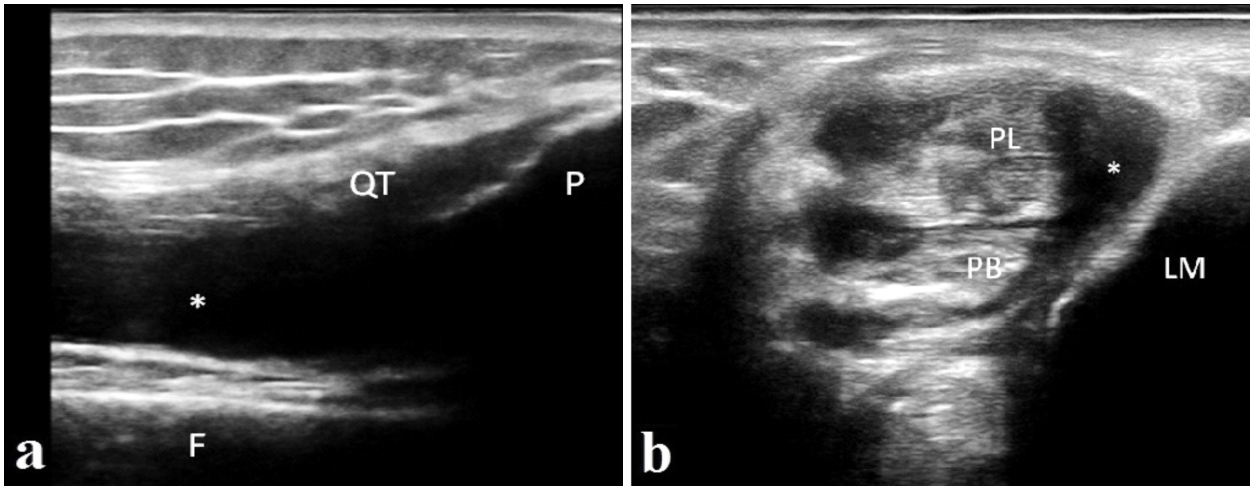

Figure 2 – ***US image in longitudinal section of the anterior aspect of the knee (a) showing moderate distension of the suprapatellar recess due to anechoic grade 2 effusion (asterisk); (b) Transversal section of the peroneal tendons showing moderate distension of the tendon sheath (asterisk) by grade 2 tenosynovitis. F: Femur; P: Patella; QT: Quadriceps tendon; PL: Peroneus longus; PB: Peroneus brevis; LM: Lateral malleolus.***

Tonsil tissue specimens had some common macroscopic features including surface congestion, hypertrophy and caseum filled crypts. Histopathology analysis of the seriate sections revealed certain morphological changes of the tonsil tissue due to the local inflammatory process. In each case, representative samples were obtained in order to visualize overall structure of the lymphoid follicles, interfollicular space, surface epithelium and crypt epithelium.

The main feature seen in the surface and crypt epithelium was lymphocytic infiltration among the squamous epithelial cells. This feature was observed in all cases in various degrees, which could be broadly classified as mild, *i.e.*, scattered lymphocytes in the epithelium, or moderate if lymphocytes were visible in groups. Thus, of the 13 specimens studied, 62% (eight cases) had a mild lymphocytic infiltration in the epithelium, 38% (five cases) featured moderate degree of infiltration, of which two cases displayed a more diffuse lymphocytic infiltration having a quasi-total extension throughout the epithelial cells (Figure 3a). Less frequent changes at this site were microabscesses, which led to a defect in the surface epithelium. Similar patterns of lymphocytic infiltration were seen also in the interfollicular spaces.

Another common pathological finding was the thickening of the tonsillar septa due to chronic inflammatory status (Figure 3b).

Most tonsillar crypts were filled with cellular debris, degenerated cells and had an overall elongated and sinuous aspect (Figure 4). Lymphoid follicles displayed varying sizes, some hyperplasic (Figure 5). This was attributed to the increased germinal center (GC) activity, *i.e.*, lymphocytic proliferation, due to the local inflammatory status.

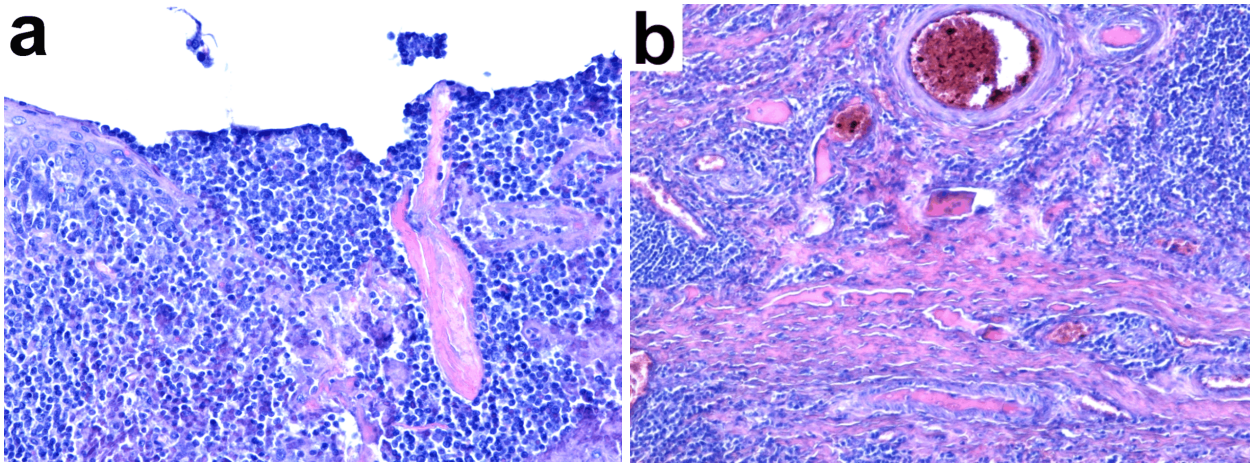

Figure 3 – ***Epithelium of tonsil crypt (a) showing diffuse lymphocytic infiltration leading to loss of normal stratified morphology of the epithelium and direct contact between lymphoid tissue and lumen of crypt; (b) Thick tonsillar septa containing a high number of collagen fibers due to prolonged inflammatory status. HE staining, ×100 (a and b).***

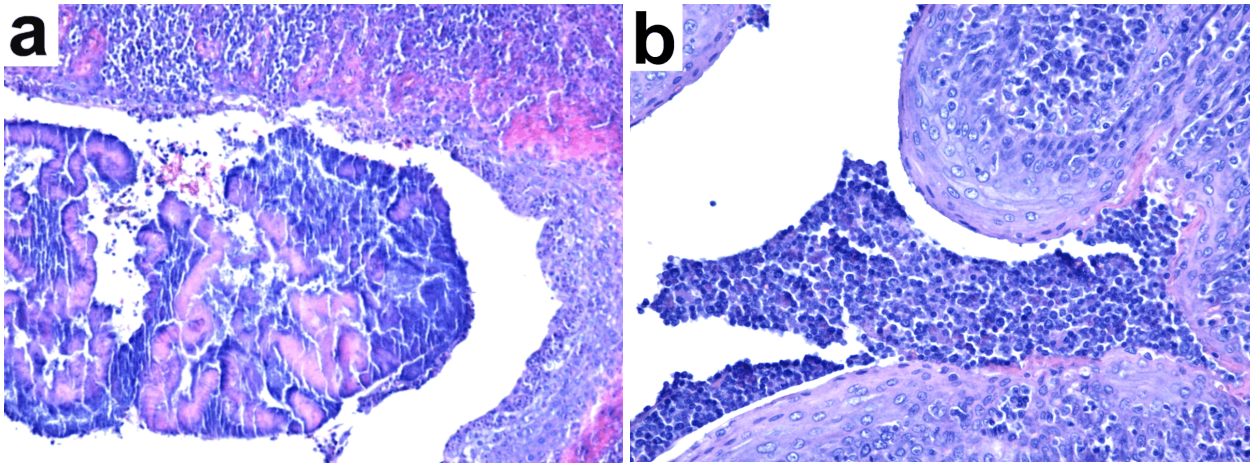

Figure 4 – ***Enlarged tonsil crypt (a) containing a large quantity of cellular and tissue debris; (b) Detailed features of crypt lumen filled with a mass of infiltrated lymphocytes. HE staining: ×100 (a); ×200 (b).***

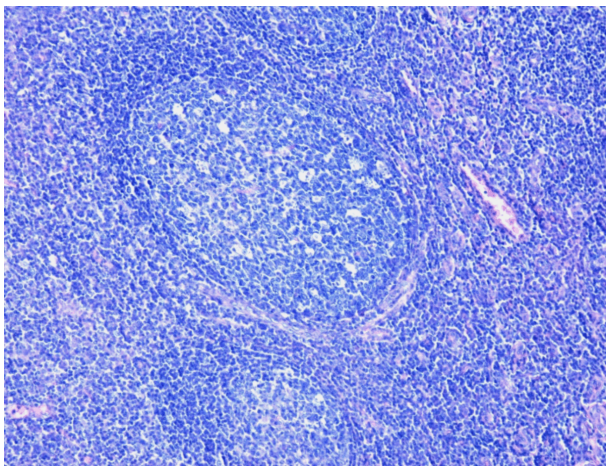

Figure 5 – ***Lymphoid follicle hypertrophy with an enlarged clear germinal center, numerous macrophages within and reduced lymphoid corona, histological changes characteristic of chronic inflammation. HE staining, ×100.***

IHC study provided further details about the distribution of lymphocytic CD20+ B-cell and CD3+ T-cell subpopulations. We could observe a typical cellular pattern of the lymphoid follicle, which commonly displayed a predominant B-cell population in the GC (Figure 6a) and peripheral distribution of T-cells. Also, hyperplasic GC featured more dense CD20-positive reactions due to increased proliferation. When analyzing the epithelial lymphocytic infiltration distribution, most cases featured more intense CD20 reactions, as opposed to CD3, attributed to the increased B-cell intraepithelial migration. Distribution of CD20+ B-cells increased in relation to the overall lymphocytic infiltrate. CD3+ reactions were visible, in addition to the cortical areas of follicles, in the interfollicular spaces (Figure 6b) and also in the surface epithelium, but to a lesser degree than the CD20+ B-cells. Immunolocalization of macrophages through CD68 staining revealed an extensive distribution. The greatest density of CD68+ cells was commonly seen in the crypt

epithelium. Most specimens revealed also patterns of mild to moderate CD68+ reactions in the GCs (Figure 7) and more intense reactions in the subepithelial and surface epithelium areas.

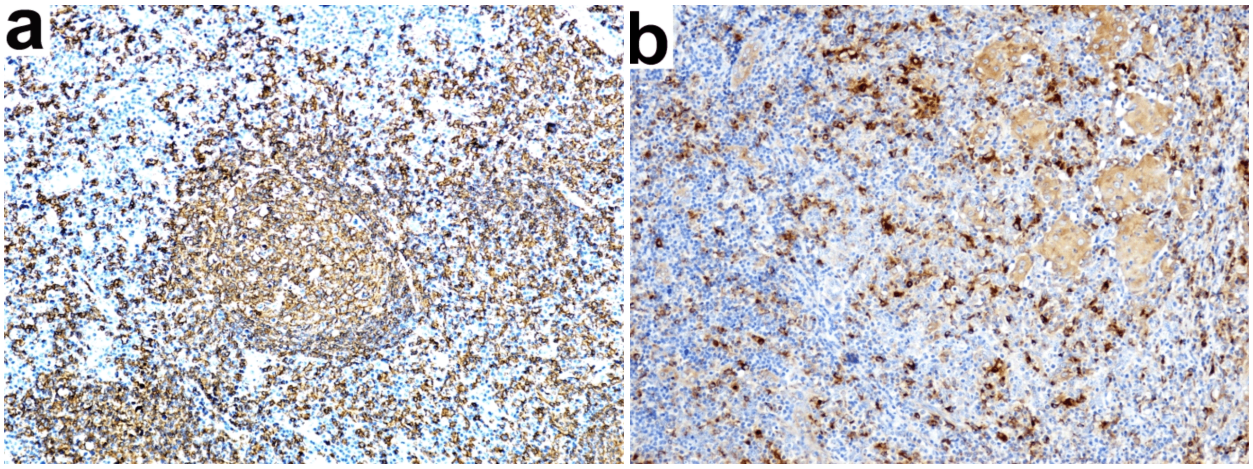

Figure 6 – ***Immunohistochemical study of tonsillar tissue (×100): (a) B-lymphocytes' distribution using CD20 immunostaining displays an intense reaction in the center of the tonsillar follicle; (b) CD3 immunostaining for T-lymphocytes showing positive reactions mainly in the interfollicular area.***

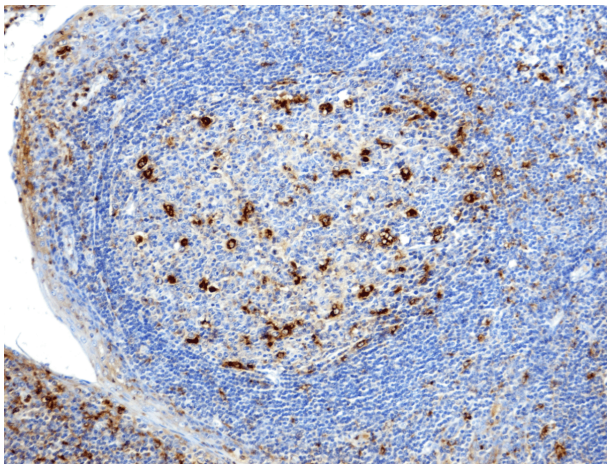

Figure 7 – ***Moderate infiltration of tonsillar germinal center with macrophages on CD68+ immunostaining (×100).***

Discussion

Palatine tonsils, together with the other lymphoid structures forming the Waldeyer's ring, are the site of initial encounter with various pathogens entering the respiratory and digestive tract. The tonsillar lymphoid tissue plays an important role in the immune defense, this interaction between foreign antigens and immune system being favored by the presence of multiple tonsillar crypts, which are enriched in immunocompetent cells [12]. Approximately one third of tonsillitis cases are caused by bacteria, most common agent being group A β-hemolytic *Streptococcus pyogenes* [13]. GAS plays and important role in the various post-streptococcal infection sequelae, such as ARF, acute glomerulonephritis and PSRA [1].

Many studies have focused on the histopathology features related to tonsillar tissue inflammation and also differentiation between chronic tonsillitis, recurrent tonsillitis and tonsillar hypertrophy. According to Zhang *et al.* [14], the main differentiating feature between chronic tonsillitis and tonsillar hypertrophy is the mean follicle area and not the mean follicle number, while Gorfien *et al.* also described a similar difference in the GC area [15]. Normal palatine tonsils are covered by a stratified squamous non-keratinized epithelium, which is avascular and normally houses only a few non-epithelial cells [16]. Some studies have outlined the principal features related to chronic tonsillitis, which include lymphoid hyperplasia, distension of the crypts (cryptitis) and fibrosis of the parenchyma [17, 18]. Uğraş & Kutluhan concluded that changes in the surface epithelium consisting of slight-to-moderate lymphocytic infiltrate, intraepithelial micro-abscess and/or diffuse lymphocytic infiltrate are reliable histopathological criteria for diagnosis of chronic tonsillitis [17]. We also noted some of these features on our study. In most of the tonsil specimens, lymphocytic infiltration of the surface and crypt epithelium was present, along with hyperplasia of the GC and in some cases fibrosis. IHC description of the epithelial infiltrate revealed sub-populations of B-cells, T-cells and also macrophages, with the former being the most prevalent. Similarly, Ruco *et al.* described the distribution pattern of mononuclear cell in chronic tonsillitis epithelium and also hinted to some possible factors responsible for B-cell migration. They studied the expression of adhesion molecules ICAM-1 and VCAM-1 by epithelial cells and also the presence of epithelial basement membrane interruptions which can facilitate the leukocyte migration [12].

GAS is a β-hemolytic, Gram-positive pathogen and one of the predominant causes of tonsillopharyngitis. Clinical signs of tonsillopharyngitis are sore throat, cervical lymphadenopathy and fever. Antibiotic treatment is highly recommended in order to avoid the post-infectious sequelae [11]. The percentage of chronic GAS carriers is relatively high in children, approximately 20% having persistence of GAS without infection or immune response [19]. By comparison, in the adult population this percentage decreases significantly. In a one-year multicenter study on 2626 patients, only 2.3% were of patients between 14 and 44 years old were non-symptomatic GAS carriers [20].

Because the signs and symptoms of GAS pharyngitis broadly overlap with symptoms of viral etiology, various

laboratory tests are used in order to confirm the GAS strain infection [11]. Culture from a throat swab remains the standard method of detecting GAS pharyngitis with a very high sensitivity, but with a significant delay in obtaining the result [11]. A faster confirmation can be obtained through RADTs, which consist of direct detection of the group A-specific carbohydrate antigen in throat swabs by agglutination methods or immunoassays [21]. Although prompt antibiotic treatment is required, it will not completely abolish the immune response to streptococcal antigens. Retrospective diagnosis of GAS disease can also be confirmed by serological methods, the most widely used being ASLO and anti-DNase B [22, 23]. If tonsil specimens are obtained, additional tissue colonization diagnosis is made through either Gram staining, although non-specific, or through immunofluorescence detection methods using antibodies for GAS [24].

Among the post-streptococcal articular diseases, ARF and PSRA are considered separate clinical entities, with some hypothesizing that PSRA is a subtype of the former. Generally speaking, PSRA has a much milder clinical picture. It is commonly defined as ReA secondary to GAS throat infection in the absence of sufficient criteria for ARF [3]. Proposed criteria for PSRA diagnosis recommended by Ayoub & Ahmed [9] include acute non-migratory arthritis that can affect any joint and is poorly responsive to NSAIDs, evidence of GAS infection and no other major Jones criteria for ARF [2]. Arthritis in PSRA has a lower-limb predominance and more frequent involvement of small joints and axial skeleton as opposed to ARF [25]. While ARF shows single peak at 12 years, PSRA patients display a bimodal peak between 8–14 years and 21–37 years [26]. Another distinction is described in terms of latency period between streptococcal infection and onset of arthritis, which is shorter in ARF, varying between 10 and 14 days [4, 26].

Association between HLA-B27 and PSRA has been reported [5]. In a review by Mackie & Keat [27], out of 36 patients typed for HLA-B27, six (16.6%) had a positive result. Very few case reports and case series report the development of sacroiliitis in both HLA-B27 positive [6] and HLA-B27 negative PSRA patients [27]. Enthesitis and tenosynovitis can also occur in the setting of PSRA, with varying prevalence, even up to 72% [4, 28]. In the review by Mackie & Keat, out of 180 identified PSRA patients, none had chorea or erythema marginatum and only four (2%) cases developed carditis [27], while a study by van Bemmel *et al.* [29] concluded that PSRA patients have a risk for carditis of about 8%. These clinical features support the idea that PSRA can be considered a subtype of ARF, lacking major clinical manifestations, which also shares features of HLA-B27 spondyloarthropaties.

Causal role of streptococcal infection is still debated. Although GAS infection is the most prevalent etiology encountered, other streptococcal strains and also non-streptococcal tonsillitis can associate PSRA clinical picture [27, 30]. The range of streptococci identified in PSRA patients seems to resemble that found in normal children with uncomplicated pharyngitis. This has led to the idea that tonsillitis itself can be the crucial precursor to arthritis and not a specific microbial agent [27, 31]. Antibiotherapy for the acute episode of bacterial tonsillitis is the generally accepted treatment choice and, in the case of ARF, a long-term secondary antibiotic prophylaxis is recommended. In PSRA, there is little consensus on initiation of long-term prophylaxis. Some studies suggest that recurrence of arthritis is rarer in patients who received prophylaxis [27]. The *American Heart Association* (AHA) *Scientific Statement* recommends a careful observation of PSRA patients for development of carditis. According to AHA, if valvular disease is detected, patients will be classified as ARF and should then receive secondary antibiotic prophylaxis [32]. In our study group, all the patients received short-term antibiotherapy without prophylaxis. We opted for a maintenance immunosuppressive treatment with Sulphasalazine 2 g to 3 g per day. On six months follow-up, no recurrence and no persistent chronic arthritis were reported.

Conclusions

This study offered an overall approach to patients diagnosed with PSRA, a still heterogeneous clinical entity. PSRA should be considered in the differential diagnosis of arthritis, mainly in young adults with arthritis of the lower-limb. Musculoskeletal US is a very useful tool in the extension of the clinical exam in order to offer a more precise characterization of joint and tendon involvement. Further research of histological and immunohistochemical description of tonsil tissue specimens in patients with PSRA may explain the role of GAS infection and lymphatic tissue on the local and systemic immunoinflammatory response. There are still some important topics that need to be addressed such as the exact causal role of GAS infection or the optimal treatment approach.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Anca-Emanuela Muşetescu and Marius Florea equally contributed to the study design and manuscript proofing.

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Corresponding author
Ştefan-Cristian Dinescu, MD, PhD Student, Department of Rheumatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40786–025 217, e-mail: stefandinescu@yahoo.com

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