

Relapsing polychondritis in a liver transplant recipient

A case report

Anna Mydlak, MD^a, Dariusz Soldacki, MD, PhD^b, Bartosz Foronczewicz, MD, PhD^b, Zygmunt Stopa, MD, PhD^a, Agnieszka Powalá, MD, PhD^c, Tadeusz Budlewski, MD, PhD^d, Leszek Pączek, MD, PhD^{b,e}, Krzysztof Mucha, MD, PhD^{b,e,*}

Abstract

Rationale: Relapsing polychondritis (RP) is a multisystemic, progressive disease of unknown etiology characterized by recurrent inflammation and progressive cartilage destruction. It can involve all types of cartilage including ears and nose, tracheobronchial tree, joints, and any other tissue rich in proteoglycans such as heart, eyes, and blood vessels. Recurrent chondritis can be life-threatening if the respiratory tract, heart valves, or blood vessels are affected. To date there is no data in the literature on the post solid organ transplantation RP.

Patient concerns: We present a 59-year-old male liver transplant recipient with primary sclerosing cholangitis who developed RP of the earlobes and nose despite post-transplant immunosuppression.

Diagnoses: Based on the clinical criteria, scintigraphy and biopsy from the left auricle his condition was diagnosed as RP.

Interventions: Pulses of methylprednisolone followed by high-dose oral steroids along with azathioprine were administered.

Outcomes: Such therapy diminished local cartilage inflammation, improved patient's general condition and the laboratory results. Significant loss of ear cartilage and characteristic "saddlenose" were observed after remission of acute symptoms. The control scintigraphy proved very good treatment response.

Lessons: To the best of our knowledge this is the first report on the RP in liver transplant recipient. Based on our patient presentation, we suggest that RP should be suspected in any transplant recipient with cartilage inflammation, and that the Michet's clinical criteria and scintigraphy seem to be the best diagnostic tools for solid organ transplant recipients suspected of RP.

Abbreviations: AZA = azathioprine, CsA = cyclosporine A, H&E = hematoxylin and eosin, IS = immunosuppression, LT = liver transplantation, P = prednisone, PSC = primary sclerosis cholangitis, PTLN = post-transplant lymphoproliferative disorders, RP = relapsing polychondritis, SPECT = single-photon emission computed tomography.

Keywords: immunosuppression, liver transplantation, relapsing polychondritis, scintigraphy

1. Introduction

Relapsing polychondritis (RP) is a rare, progressive, and potentially lethal autoimmune disease.^[1] Its prevalence is about 3.5 cases per million and it occurs most frequently in the fourth

and fifth decade of life.^[2–4] The etiology of RP remains unknown, but its pathogenesis involves autoimmune reaction to type II collagen present in the cartilage tissue.^[5] It was reported, that one of the factors inducing autoimmune reaction is matrilin non-collagenous matrix protein, which is primarily present in thyroid cartilage, earlobes, and nose of adult individuals.^[6,7] Recurrent inflammation of cartilages leads to their progressive destruction.^[8] This condition may involve not only different cartilage types, but also structures that are rich in proteoglycans, such as eyeballs, heart, blood vessels, the inner ears, or kidney glomeruli.^[9] Therefore, the clinical presentation of the disease may be highly variable. Moreover, frequent overlapping with other autoimmune diseases can additionally hamper establishing final diagnosis.^[9–11]

The first symptoms are usually nonspecific, and may include pyrexia, weakness, body mass loss, or drowsiness. At the acute phase the biochemical markers of inflammation (eg, elevated C-reactive protein, erythrocyte sedimentation rate, and leukocytosis), normocytic anemia, and/or polyclonal hypergammaglobulinemia can be observed.^[7–9] Further disease development and its clinical picture depend on the location of cartilage damage, other organs involvement, and comorbidities.

The auricular chondritis is the most frequent location and is considered specific for RP. It is found in 20% of patients at the disease onset and in 90% during disease duration.^[11] Currently,

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^a Department of Cranio-Maxillofacial Surgery, Oral Surgery and Implantology, Medical University of Warsaw, ^b Department of Immunology, Transplantology and Internal Diseases, Medical University of Warsaw, ^c Department of Pathology, Medical University of Warsaw, ^d Nuclear Medicine Unit, Department of Diagnostic Radiology, Central Clinical Hospital Ministry of Internal Affairs, ^e Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland.

* Correspondence: Krzysztof Mucha, Department of Immunology, Transplantology and Internal Diseases, Medical University of Warsaw, Nowogrodzka 59, 02-006 Warsaw, Poland (e-mail: kjmucha@gmail.com).

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the RP diagnosis is based on characteristic clinical manifestations and criteria that have been established previously by McAdam et al and modified by others.^[12,13] Positron emission tomography/computed tomography was found to have a growing role in the RP diagnosis and follow-up.^[14]

According to McAdam, if 3 or more clinical features out of 6 of the following: bilateral auricular chondritis, nonerosive seronegative inflammatory arthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis, and audiovestibular damage are positive, the diagnosis may be set even without biopsy confirmation. Modifications proposed later aimed at faster diagnosis and therapy implementation. Patients with mild disease activity are usually treated with nonsteroidal anti-inflammatory drugs and/or small doses of prednisone (P). Those with severe manifestations require high steroid doses alone or in combination with immunosuppressive drugs. Azathioprine (AZA), cyclosporine A (CsA), methotrexate, and plasmapheresis have all been reported as effective therapies. More recently, biological therapies have also been tried in RP, and anti-CD4 chimeric monoclonal antibody has been proven successful.^[15] We can speculate that the immunosuppression (IS) used to prevent graft rejection, may also prevent RP development in undefined number of organ transplant recipients. This might be a reason why the literature data on the post solid organ transplantation RP is so scarce.

2. Case report

A 59-year-old male presented to the clinic with the symptoms of RP. His medical history included liver transplantation (LT) in 2005 for the end-stage primary sclerosing cholangitis (PSC) diagnosed 1 year earlier, and ulcerative colitis (UC) since 2000. Post-LT IS consisted of P and CsA initially in induction, later in maintenance doses were given concomitantly with sulfasalazine.

He developed first signs of RP in May and June 2015 when he suffered from rhinitis, followed by the reddening, swelling, and pain of his left earlobe in August. The primary care physician ordered him the empiric treatment with clindamycin, amoxicillin, and lincomycin, but no significant improvement was achieved. On admission, the entire hall of the left ear was swollen, red, hot, and painful even at the slight contact. The earlobe was spared (Fig. 1A and B). The involvement of the nasal cartilage presented with pressure tenderness of the nasal base. The diagnostics of

other organs involvement was negative. The whole body scintigraphy and single-photon emission computed tomography (SPECT/CT) at 4 and 24 hours after administration of 740 MBq dose of ^{99m}Tc-Techimmuna, revealed increased marker accumulation in auricles and nasal septum (Fig. 2). The peripheral blood tests revealed an increased white blood cell and neutrophil counts (13.6 and 9.16 G/L, respectively), elevated erythrocyte sedimentation rate (86 mm/h), C-reactive protein (97.3 mg/L), and hypergammaglobulinemia. The liver and kidney function tests remained normal. *Klebsiella oxytoca* and *Candida albicans* were isolated from affected external ear. Accordingly, antibiotic was administrated intravenously and daily P dose was increased to 15 mg.

Because of no response to treatment, a biopsy from the left auricle was taken for microbiologic and histopathologic examinations. The latter analysis revealed: large, polymorphic cartilage infiltration composed mainly of polyclonal plasmocytes, B (CD20⁺) and T (CD3⁺) lymphocytes as well as small amounts of eosinophils and neutrophils. Epstein-Barr virus (EBV) antigen LMP1 was negative, and no dendritic cells (CD23⁺) were detected. Mild infiltration of T lymphocytes to cutaneous structures was observed (Fig. 3A–C). In overall, the examination supported rather the diagnosis of nonspecific chronic inflammation than the primary cartilage disease and excluded, for example, post-transplant lymphoproliferative disorder (PTLD). The consecutive microbiological tests turned negative. The dose of P was increased to 30 mg/day and remaining therapy was maintained, but patient's clinical condition gradually worsened and the inflammation of the right auricle progressed (Fig. 4).

While excluding the diseases that would contraindicate IS increase, such as infections, PTLD, and other malignancies, the diagnosis of RP was set based on the Michet's modified criteria. Therefore, pulses of methylprednisolone followed by high-dose oral steroids along with AZA were administered. It diminished local cartilage inflammation and improved patient's general condition and the laboratory results. Significant loss of ear cartilage and characteristic "saddle-nose" were observed after remission of acute symptoms (Fig. 5). The control scintigraphy and SPECT proved very good treatment response.

The Ethics Approval/IRB was not required for this study.



Figure 1. Inflammation of the left auricular cartilage at admission. The swollen hall of the left ear (A). Spared right ear and left earlobe (B).

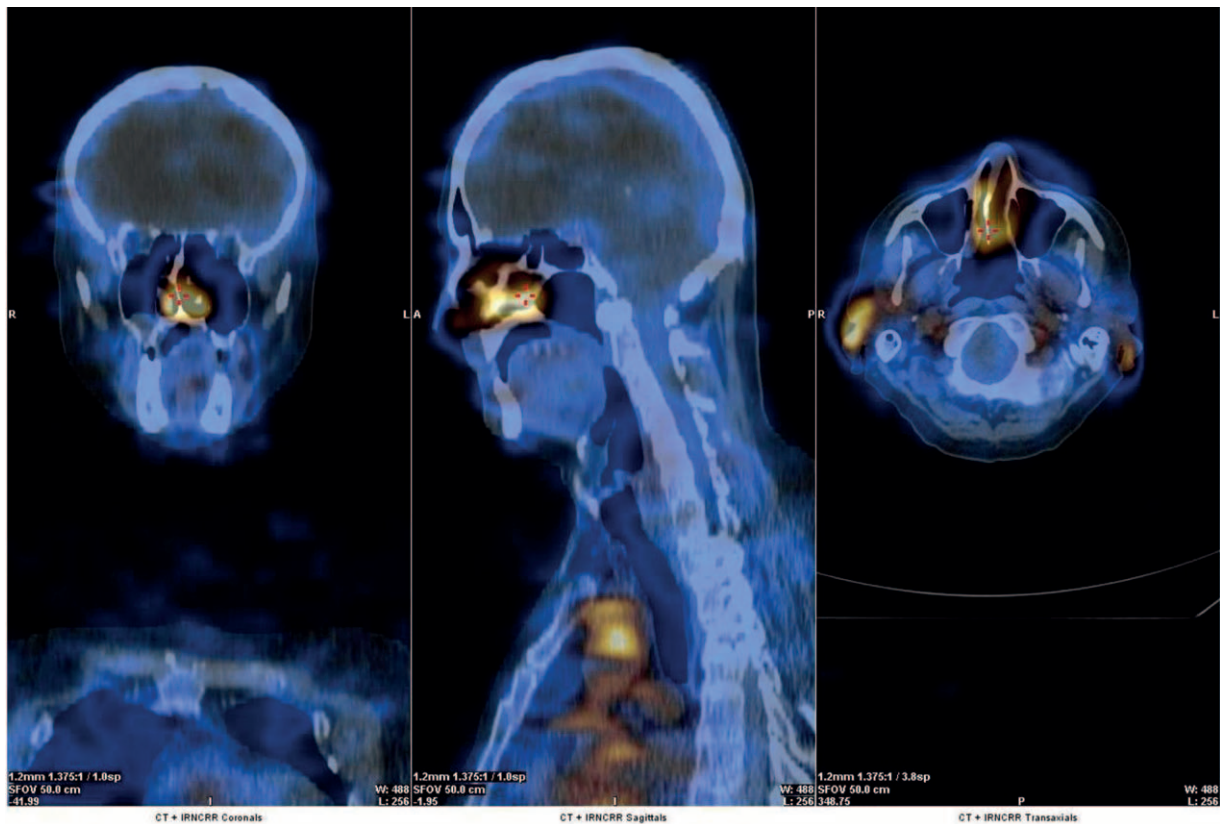


Figure 2. Scintigraphy: increased marker accumulation in auricles and nose. Visible radioactivity in lungs as well as heart, liver, and large vessels, is typical for scintigraphy test with the usage of radiopharmaceutical. The examination does not show inappropriate accumulation of contrast in lungs, trachea, and bronchi.

3. Discussion

To the best of our knowledge, this is the first report on the RP that occurred in LT recipient. The concerns related to the autoimmune diseases recurrence and de novo development after transplantation are not new. Previously, we proposed a scenario for another immunology-related disease—psoriasis—recurrence after LT in which IS does not inhibit all immune or inflammatory pathways of the disease, enabling the disease recurrence in selected patients despite continued IS.^[16] We found that coexisting other autoimmune diseases may predispose to disease development.

Presented patient had 2 autoimmune comorbidities, PSC and UC, which could have precipitated the RP development.

However, we cannot be completely sure whether RP in our patient developed de novo post LT, or recurred induced by preceding infection. To diagnose the recurrence of any disease, it is mandatory to know if this disease was present in the past—in this case—before LT. In the medical history of presented patient there were no symptoms of RP. So, it is more likely that it developed de novo. His first symptoms followed the upper respiratory tract infection with auricular and nasal cartilage inflammation. These 2 locations are typical for RP, therefore it was suspected early at the hospital admittance. However, the final diagnosis required ruling out other diseases and fulfilling the RP diagnostic criteria. The first condition was managed by classical patient internal diagnostic work-up. The second was

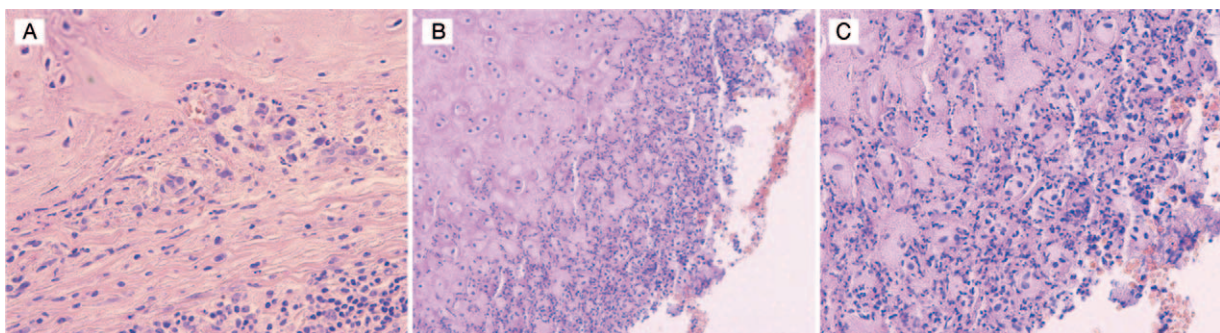


Figure 3. Deep inflammatory infiltration of the subcutaneous tissue and superficial cartilage pinna. Infiltrations including plasma cells and few neutrophils (H&E $\times 200$) (A). Control biopsy after 1 mo: dominating inflammation containing numerous neutrophils and fewer plasma cells and lymphocytes: (B) H&E $\times 100$ and (C) H&E $\times 200$.



Figure 4. Inflammation of the right auricular cartilage.

possible because of the 3-phase scintigraphy. It seems to be safe diagnostic method; however its use for monitoring may be debatable. It carries a risk for human antimurine antibodies (HAMA) formation, serum disease development, and false negative results. On the other hand, this effect is uncertain when IS is used.

The involvement of 2 cartilages confirmed both clinically and by scintigraphy still did not fulfill standard McAdam's criteria. According to the later Damiani and Levine modification, to correctly diagnose RP, 1 out of the 3 criteria has to be satisfied: 3 of McAdam's criteria; at least 1 of McAdam's criteria and a positive pathologic confirmation; 2 of McAdam's criteria and positive response to the administration of corticosteroids or dapsons.^[4,13] The presented patient satisfied only the third criterion, because histopathologic examination was inconclusive and unspecific for RP. Unfortunately, the fulfillment of the third Damiani and Levine criterion was possible only after successful treatment. Therefore, it did not facilitate the therapeutic decision. In contrast, the latest and currently recommended Michet's modifications allow the RP diagnosis if 1 out of the following criteria are satisfied: inflammation of 2 out of 3 cartilages in auricles, nose, larynx/bronchus; inflammation of 1 out of 3 cartilages in auricles, nose, larynx/bronchus + symptoms of inflammation on 2 other organs.^[4,12] The presented patient has satisfied the first Michet's criterion and was successfully treated thereafter.

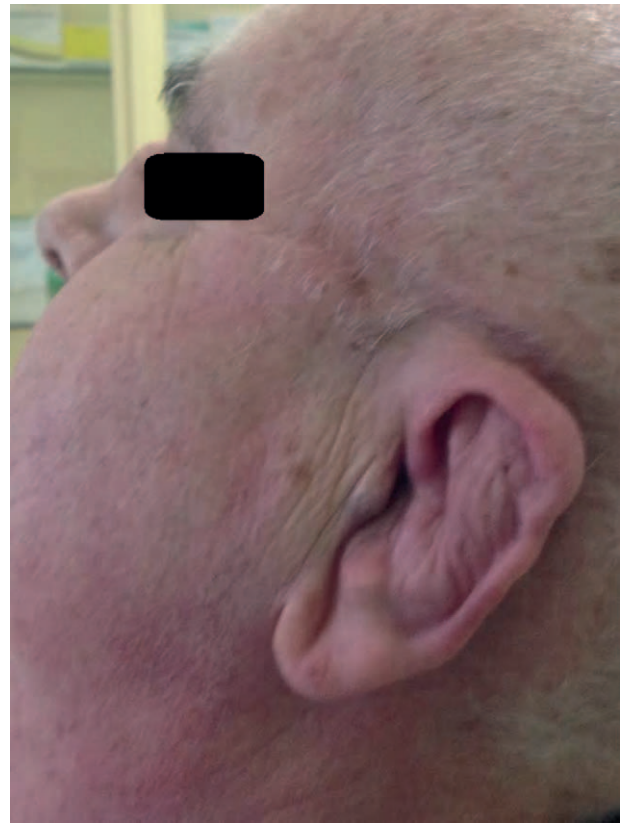


Figure 5. Loss of the ear and the nose cartilage with characteristic "saddle-nose" deformation.

4. Conclusion

In conclusion, RP, although rare, is a progressive and potentially lethal autoimmune disease. Based on our patient presentation, we suggest that:

- 1) RP may develop despite IS and should be suspected in any transplant recipient with cartilage inflammation;
- 2) the Michet's criteria seem to be the best for solid organ transplant recipients, allowing prompt diagnosis and therapy; and
- 3) scintigraphy seems to be useful and safe diagnostic tool if RP is suspected, especially in transplant recipients.

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