OLGU SUNUMU CASE REPORT

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Relapsing Polychondritis Misdiagnosed and Treated as a "Soft Tissue Infection" and a Brief Review of Diagnostic Clinical Clues

"Yumuşak Doku Enfeksiyonu" Şeklinde Yanlış Tanı ve Tedavi Almış Bir Tekrarlayan Polikondrit Olgusu ve Tanısal Klinik İpuçlarının Gözden Geçirilmesi

Özgür GÜNDÜZ,[a]
Serkan DEMİRKAN,[a]
Güzin SAMAV,[a]
Hakan ARSLAN,[a]
Rebiye ÇAKARTAŞ[a]

[a]Department of Dermatology and Venerology,
Kırıkkale University Faculty of Medicine, Kırıkkale

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Yazışma Adresi/*Correspondence:*
Özgür GÜNDÜZ
Kırıkkale University Faculty of Medicine, Department of Dermatology and Venerology, Kırıkkale, TURKEY/TÜRKİYE
gunduzozgur@windowslive.com

ABSTRACT Relapsing polychondritis (RPC) is a rare immune-mediated disease, which targets particularly the cartilaginous tissue. At the initial stages of RPC, recurring mild-inflammatory attacks targeting the ears, nose, eyes, joints and respiratory tract can be observed but as the disease progresses, aortic and/or mitral valvular regurgitation (AR/MR) or life-threatening tracheobronchomalacia (due to involvement of aortic, mitral valves and/or trachea) may occur, as well as severe destruction of the ear, nose, etc. RPC may coexist with other diseases, such as systemic vasculitides, Graves disease or myelodysplastic syndrome. Establishing an early diagnosis is of utmost importance to prevent the development of AR/MR, or tracheobronchomalacia by preserving the cartilage tissue and also to diagnose a possible coexisting disease. Patients, particularly at the initial stages of the disease may object to a skin biopsy due to concerns for visible scars. Therefore, a good grasp of RPC's clinical symptoms may facilitate to establish an early diagnosis.

Keywords: Polychondritis, relapsing; otitis externa; diagnosis; diagnosis, differential

ÖZET Tekrarlayan polikondrit (TP), özellikle kıkırdak dokuyu hedef alan, nadir görülen immün sistem aracılı bir hastalık tablosudur. TP genellikle ilk aşamada kulak, burun vb. dokularda tekrarlayan düşük şiddetli inflamatuar ataklara yol açarken ileri evrelerinde, hem bu dokularda ileri derecede yıkıma sebep olabilir ve aynı zamanda aort, mitral kapak, trakea vb. dokuları etkileyerek aort/mitral kapak yetmezlikleri ve trakeomalazi gibi hayatı tehdit edebilen tablolar oluşturabilir. TP'ye; Graves, sistemik vaskülitler, miyelodisplastik sendrom gibi başka hastalıklar da eşlik edebilir. TP'nin erken tanınması kıkırdak dokunun korunarak aortik/mitral yetmezlikler, trakeomalazi gibi hastalıkların gelişmesinin engellenmesi ve muhtemel eşlik eden diğer hastalıklara erken müdahale edilebilmesi açısından faydalıdır. Çoğu hasta, erken evrelerde görünür iz kalabileceği endişesiyle biyopsiye onay vermeyebilir. Bu yüzden TP'in klinik semptomlarının bilinmesi, erken ve ayırıcı tanıyı kolaylaştıracaktır.

Anahtar Kelimeler: Polikondrit, tekrarlayan; otitis eksterna; tanı; tanı, ayırıcı

Relapsing polychondritis (RPC) is a rare immune-mediated condition, which targets particularly the cartilaginous tissue. RPC frequently attacks the ears, nose, eyes, joints and respiratory tract, but heart, kidneys may also be affected. The diversity of the affected anatomic regions and organs leads to a wide spectrum of clinical manifestations, which range from an occasional auricular inflammation to aortic and/or mitral valvular regurgitation or life -threatening tracheobronchomalacia.[1] RPC may coexist with other diseases, such as systemic vasculitides, Graves' disease or myelodysplastic syndrome. As of today, there are no established clinical or laboratory findings to predict the disease's outcome.

CASE REPORT

A 41-year old female presented with an earache and a past medical history of recurrent ear infections. At the time of admission, she was noted to have a red, painful, edematous swelling on her left auricula, which spared the ear lobe (Figure 1). 10 weeks prior, she had developed transient cough. Seven weeks later, an acute, painful, swelling occured on her left ear. She was evaluated by an otolaryngologist and diagnosed with *"swimmer's ear"* and started on antibiotics. After two weeks, despite the treatment with ciprofloxacillin, there was no relief from her symptoms.

Her medical history revealed that the patient's complaints about her ears had started 3 years ago. Initially, her right ear was affected. Her symptoms were similiar to the current ones and she had been treated with amoxicillin plus clavulanic acid combination. Over the time, she started to have intermittent episodes of cough and rhinorrhea, intermittent painful redness in the eyes, recurrent swellings on her right ear, which were diagnosed as "otitis externa" and pain in the knees and ankles. She was also diagnosed with arthritis and was prescribed nonsteroid antiinflammatory drugs.

Laboratory tests revealed a sedimentation rate of 67 mm/hr (0-20 mm/hr), a C-reactive protein rate of 48.75 mg/L (0.15-5.0 mg/L), a mean corpuscular volume of 77.8 fL (78.0-105.0). Anti nuclear antibodies, rheumatoid factor, creatinine, blood urea nitrogen, liver enzymes were unremarkable.

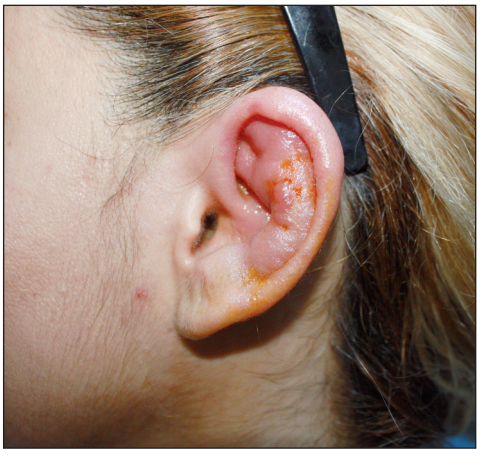

FIGURE 1: Erythema and edematous swelling of the left ear. The inflammation dominantly covers the helix and abruptly ends with a sharp demarcation line, sparing the left lobule.

Based on her history and clinical examination (recurrent auricular inflammation on both ears, nonerosive arthritis, recurrent ocular inflammation), her preliminary diagnosis was "recurrent polychondritis". She was consulted to departments of physical therapy and rehabilitation, rheumatology and started on methylprednisolone 40 mg/d. After one week, the auricular inflammation was significantly regressed.

DISCUSSION

RPC is an immune-mediated, multisystemic inflammatory disease that leads to degenerative changes in the connective tissue. RPC may present within a wide spectrum of diverse clinical manifestations, depending on the extent and the severity of the affected connective tissue. The etiology of RPC is unknown. Various studies indicate an association between HLA-DR4, HLA-DR6 and RPC.[1,2] Hue-Lemoine and et al. also identified a new set of genes, DQB1*0601, DQA1*0103, to be associated with RPC.[3] Coexistence of RPC and various other diseases; endocrine (Graves, Hashimato thyroiditis, Diabetes mellitus, etc.) inflammatory bowel diseases, systemic vasculitides (ANCA-associated, polyarteritis nodosa, Behcet's disease, necrotizing vasculitis, etc) and an increased prevalance of myelodisplastic syndromes are reported.[4-6] RPC is also reported to manifest after an intravenous injection of a mixture, which consisted of hydrochloric acid, carburetor fluid, tap water, and internal matrix of a nasal inhaler.[7] Diversity of the clinical symptoms, associated genes and coexistent diseases indicate the possibility of RPC being a syndrome rather than a single, uniform disease.

Several study results point out a possible autoimmunity in RPC patients. Autoantibodies to type II collagen, extracellular matrix components of cartilage have been identified and there are also reports about a possible T cell-mediated reaction to cartilage components in patients with RPC.[8,9] Specific T-cell clones for peptide corresponding to residues 261–273 of the type II collagen molecule has beeen reported in a patient with RPC by Buckner et al.[10] Imbalance of T lymphocyte subsets has also been reported.[11]

Pathogenesis of RPC is unknown. Working hypothesis proposes that following a damage of connective tissue, particularly cartilage tissue, by yet-unidentified factors, certain epitopes or antigenic molecules are exposed to the immune system of genetically preconditioned individuals. This leads to formation of antibodies to certain molecular components of cartilage and abnormal proinflammatory cytokine production, causing tissue damage. Further support to this hypothesis comes from the case reports, which describe development of RPC after pinna piercing and glucosamine chondroitin ingestion.[12,13]

According to the aforementioned working hypothesis, the initial antigens, are components of the cartilaginous tissue. After exposure to the immune system possibly due to a physical, infectious or biochemical insult, they trigger an autoimmune reaction. In several studies, various autoantibodies have been detected against type collagen II (CII), matrilin-1, cartilage oligomeric matrix proteins (COMPs), and collagen type-IX (CIX), X, and XI in RPC patients and animal models.[8-10,14] Various research groups succesfully recreated RPC models in animals and observed a connection between CII and several HLA groups.[15,16] Bradley et al. showed the development of auricular chondritis in HLA-DQ6/8 double transgenic mice following the immunization with collagen-II.[15] In a similar study by Taneja et al. immunized transgenic mice expressing DQ8 (DQA1*0301, DQB1*0302) in a NOD background lacking endogenous class II molecules (Abetao) with CII and observed development of polychondritis, auricular chondritis, and polyarthritis, with clinical and histological similarities to RPC in humans in 85% of NOD.DQ8 mice. CII-immunized mice has also been found to develop a T cell response and produce antibodies to type IX collagen and self-CII. B10.DQ8 transgenic mice developed polyarthritis and antibodies to CII only. The susceptibility to auricular chondritis in NOD.DQ8 mice has been proposed as response to CIX by the researchers. A higher number of activated cells, CD4+CD44(hi) CD62L(lo), and lower regulatory cells CD4+CD152 +CD25+ in NOD.DQ8 mice compared with B10.DQ8 mice were also reported.[16] T lymphocytes in a young RPC patient was found to have Th1cytokine profile.[17] Lymphocytic activation seems to induce activation of macrophage/monocyte system, since levels of serum monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-beta (MIP-1beta) and interleukin-8 (IL-8) has been observed to increase during active inflammation in RPC.[18]

Epitope spreading seems also to play a role in the RPC. At the initial stages, frequently one tissue (ear, nose) is inflammed but at the later stages, other organs, (i.e. heart, trachea, etc) can also be affected. This can be attributed to occurence of new auto-antibodies (i.e., autoantibodies to matrilin-1).

Clinical manifestations of RPC are very diverse. Auricular chondritis, arthritis, nasal chondritis, laryngeotracheal and ocular symptoms are the most frequently encountered initial manifestations.[19-21] Inflammation of the ear has been thought to be the hallmark of the RPC.[22] Chondritis of pinna is probably the most common and typical feature and is observed in 91% of men and 78% of women with RPC.[20] Overall 90% of the patients present with auricular inflammation during the course of disease.[14] Peripheral anatomic regions with profuse collagen content are also the most affected organ systems in RPC patients with advanced disease.

In addition, other systems such as large airways, heart and nervous system, may be affected. Particularly, large airway and heart involvement may have very serious and fatal outcomes (eg., tracheobronchomalasia, combined aortic and mitral valve regurgitation and myocarditis, respectively). The exact frequencies of these manifestations remain unclear. 69% of patients are estimated to have laryngeotracheal involvement.[23] Costochondritis, ocular inflammation manifested as conjunctivitis, iritis, scleritis, retinopathy, even retinal detachment, and polyarthritis affecting frequently interphalangeal joints and knees have also been reported.[20,22-24] Early stages of large airway and heart disease may be insidious. Therefore extra attention must be paid to the examination of these systems when RPC is included in the differential diagnosis.

There are no specific tests for RPC. McAdam et al. proposed 6 criteria, of which 3 must be met to eastablish the RPC diagnosis (Table 1).[19] None of

TABLE 1: McAdam's Criteria for Relapsing Polychondritis". 3 out of 6 criteria are required to establish a diagnosis.[19]

McAdam's Criteria for Relapsing Polychondritis
Bilateral Auricular chondritis
Nonerosive, seronegative inflammatory polyarthritis
Nasal Chondritis
Ocular Inflammation (conjunctivitis, keratitis, scleritis/episcleritis,uveitis)
Respiratory tract chondritis (laryngeal and/or tracheal cartilages)
Cochlear and/or vestibular dysfunction (neurosensory hearing loss, tinnitus, and/or/vertigo)

"The McAdams criteria" is pathogonomonic, so the physician should have to exclude all the other possible causes for any of them. Also, some of these criteria may not be overt, manifest slowly and even subclinically, making them hard to recognize. Another set of proposed criteria (Table 2) include histologic confirmation and positive response to steroids.[25] Due to reluctance of some patients to undergo a skin biopsy, an accurate diagnosis of RPC may depend on the recognition of the clinical symptoms and on the elimination of the other possible etiological factors (Table 3). Honne et al. proposed fluorodeoxyglucose-positron emission tomography/computed tomography as a valuable diagnostic tool for the diagnosis and evaluation of a RPC patient, who had not typical ear and nose involvement.[26] Shimizu et al. reported that inspiratory and expiratory three-dimensional computed tomography and impulse oscillation with three-dimensional color imaging may be used to evaluate the airway involvement in the RPC patients who can not perform (repeated) spirometry.[27]

Due to rarity of RPC, there is no established therapy regiments.[28] The treatment is largely em-

TABLE 2: Modified McAdam's diagnostic criteria for "Relapsing Polychondritis". 3 McAdam's criteria, 1 McAdam's criteria and histologic confirmation or 2 McAdam's criteria and steroid and/or dapson responsive multiple chondritis are required to establish a diagnosis.[25]

Modified McAdam's Criteria for Relapsing Polychondritis
At least three of McAdam 's diagnostic criteria
One or more of the clinical fndings with positive histologic confirmation
Chondritis at two or more seperate anatomic locations with response to steroids and/or dapsone

TABLE 3: Clinical and laboratory clues for the differential diagnosis of relapsing polychondritis.

	Clues for Differential Diagnosis of Relapsing Polychondritis (Excluding the Biopsy)		
Disease	**Similar Clinical Findings**	**Distinctive Clinical Findings**	**Laboratory Findings**
Soft Tissue Infection	Auricular Inflammation	Ear lobule affected Possible peripheral lymphadenopathy No relapsing-remitting course	Increased CRP, ESR Leukocytosis
Tuberculosis (Lupus Vulgaris)	Auricular Inflammation	Usually Painless Slow, asymptomatic progress Frequently one ear is affected Ear lobules	Positive culture (Löwenstein-Jensen) PPD (+)
Leprosy	Auricular Inflammation Saddle nose Deformity	Usually seen in lepramatous leprosy Accompanying numerous macules, plaques and nodules Various systemic manifestations (hepatic failure, testicular involvement, male gynecomasty etc) Sensory neuropathy	M. leprae bacilli (+) microscopy
Chondrodermatitis Nodularis Helicis	Auricular Inflammation	Solitary firm nodule located on helix or antihelix Usually on the side patient lies on in the bed Spares lobule Stays stable for months	
Wegener Granulomatosis	Saddle Nose Deformity Tracheal Involvement Eye Involvement ANCA (+)*	Mucosal Involvement of the Aformentioned Sites Pulmonary Disease (+) Renal Involvement (RPGN)** Neural system involvement (i.e., mononeuritis simplex)	p-ANCA (+)
Rheumatoid Arthritis	Arthritis Eye Inflammation	Erosive, symmetric arthritis	High RF titers High anti-cyclic citrullinated peptide titers

*Anti neutrophil cytoplasmic antibodies **Rapidly progressive glomerulonephritis.

piric and based on case reports. A combination of immunsupressive drugs are usually preferred. Arthralgias, mild auricular and/or nasal involvements are preferentially treated with non-streroidal anti-inflammatory drugs.[29,30] Dapson is also reproted to be beneficial for the cardiorespiratory involvement.[30] Severe acute attacks with a risk of end-organ damage, i.e. systemic vasculitis, severe laryngeobronchial and/or ocular involvement, should be treated with systemic steroids.[29,30] Similar to the the treatment of autoimmune diseases, steroid-sparing agents, methotrexate, azathioprine and cyclosporine have been used in the treatment of RPC and reported tohave beneficial effects.[30,31] Tumor necrosis factor-α antagonists may also be used in RPC. Improvement of laryngotracheal, nasal and auricular chondritis was reported in 18 of 31 RPC patients treated wit infliximab. Etanercept and adalimumab was also reported to beneficial. Improvement obtained with etanercept was reported to last between 9 months and 3 years.[32]

As conclusion, this case highlights a prolonged diagnostic phase (approximately 3 years) of a RPC patient and aims to familiarize the physicians with RPC. A good grasp of RPC's common manifestations may enable an early diagnosis, intervention and subsequently prevent serious organ-damage and improve the disease outcome.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Idea/Concept: *Özgür Gündüz, Serkan Demirkan, Güzin Samav, Hakan Arslan, Rebiye Çakartaş;* ***Design:*** *Özgür Gündüz, Serkan Demirkan, Güzin Samav, Hakan Arslan, Rebiye Çakartaş;* ***Control/Supervision:*** *Özgür Gündüz, Serkan Demirkan, Güzin Samav, Hakan Arslan, Rebiye Çakartaş;* ***Data Collection and/or Processing:*** *Özgür Gündüz, Serkan Demirkan, Güzin Samav, Hakan Arslan, Rebiye Çakartaş;* ***Analysis and/or Interpretation:*** *Özgür Gündüz, Serkan Demirkan, Güzin Samav, Hakan Arslan, Rebiye Çakartaş;* ***Literature Review:*** *Özgür Gündüz, Serkan Demirkan, Güzin Samav, Hakan Arslan, Rebiye Çakartaş;* ***Writing the Article:*** *Özgür Gündüz, Serkan Demirkan, Güzin Samav, Hakan Arslan, Rebiye Çakartaş;* ***Critical Review:*** *Özgür Gündüz, Serkan Demirkan, Güzin Samav, Hakan Arslan, Rebiye Çakartaş.*

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