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ORIGINAL ARTICLE

Ultrasonography of auricular cartilage is a potential tool for diagnosing relapsing polychondritis and monitoring disease activity

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Abstract

Aim: To assess the clinical utility of ultrasonography in the diagnosis and monitoring of disease activity in relapsing polychondritis (RP).

Methods: Auricular and nasal chondritis of 6 patients with RP were assessed by ultrasonography before treatment initiation. Changes in the ultrasonographic and clinical findings and serum inflammatory markers were longitudinally assessed. Ultrasonography was also performed in 6 patients with repeat ear trauma, 6 patients with auricular cellulitis and 6 healthy controls for comparison among groups.

Results: In all cases of RP, ultrasonographic findings before treatment revealed low-echoic swollen auricular and nasal cartilage and perichondral soft-tissue with increased power Doppler signals (PDS) corresponding to biopsy findings. After 2-month treatment with prednisolone (PSL) combined with methotrexate, clinical and serum inflammatory markers were completely resolved. Although swollen perichondral soft-tissue, cartilage and PDS on auricular ultrasonography were also significantly improved, PDS remained in 2 of 6 cases, which showed flare early after tapering PSL. Finally, ultrasonographic findings of RP were substantially differentiated between patients with repeat trauma and cellulitis and healthy controls based on the thickness of soft tissue around the cartilage, PDS and subperichondral serous effusion.

Conclusion: Assessment of RP lesions by ultrasonography is useful for the evaluation of cartilaginous lesions and monitoring of disease activity, especially when considering the treatment response and the timing of drug tapering.

KEYWORDS

auricle, cartilage, imaging, relapsing polychondritis, ultrasonography, ultrasound

Mitsuharu Yoshida and Yoshinori Taniguchi have contributed equally to this manuscript.

1 | INTRODUCTION

Relapsing polychondritis (RP) is a systemic inflammatory disease of unknown cause characterized by inflammation of the cartilage throughout the body. The disease occurs in patients of all ages, and cartilage of the nose and ear, articular cartilage and tracheal cartilage are common sites of onset. Particularly, auricular chondritis is the most common site of onset. Systemic complications include cardiovascular symptoms, such as aneurysm, large-vessel vasculitis and valvular heart disease; skin symptoms, such as purpura and ulcer; respiratory symptoms and, although rare, central nervous system and kidney diseases.[1,2]

Although the pathogenesis of RP has not been fully elucidated, autoimmune reactions to type II collagen are considered essential, and both humoral and cellular immunity have been implicated in the autoimmune reaction.[3–5] The association of genetic factors has also been reported, and although the association with human leukocyte antigen (HLA)-DR4 is a risk of onset of RP, HLA-DR6 has also shown a negative correlation with organ complications.[6]

Some cases of RP have atypical clinical symptoms or imaging findings and present with refractory or recurrent episodes. Because there are no specific or easily measurable markers for RP serologically and genetically, it is difficult to diagnose RP and detect an RP flare early in the course of disease.[7,8] Although previous studies have reported the usefulness of imaging tests, such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose–positron emission tomography/CT (FDG-PET/CT) and bone scintigraphy for diagnosis and assessment of disease activity,[9–16] performing these imaging tests frequently is unrealistic without careful consideration of cost, convenience, invasiveness and radiation exposure. Therefore, it is necessary to establish a more convenient and less invasive imaging modality such as ultrasonography that can be repeatedly used for diagnosis and evaluation of disease activity. A further advantage of ultrasonography is that of being available during outpatient consultation and of providing information that can be directly translated into patient management.

This study investigates the usefulness of ultrasonography in the diagnosis of RP and the monitoring of disease activity.

Key Messages

- Ultrasonography might be useful in the diagnosis and differential diagnosis of relapsing polychondritis.
- Ultrasonography can monitor disease activity and determine the treatment response in relapsing polychondritis.

2 | MATERIALS AND METHODS

Of all patients with RP who were diagnosed in our hospital between 2014 and 2019, we retrospectively reviewed 6 patients with RP who were evaluated for cartilage lesions using ultrasonography. We used the criteria proposed by Damiani and Levine for diagnosis, with RP diagnosed when one of the following 3 criteria was satisfied: (a) meets all 3 of McAdam's criteria; (b) meets one of McAdam's criteria and the pathologic findings are consistent; and (c) meets 2 of McAdam's criteria and responds to steroids or diaminodiphenyl sulfone (dapsone).[17] Noblus (Hitachi) was used as the ultrasound system for the evaluation of cartilage lesions, with a 18-MHz linear-type probe (Figure 1A and Figure S1A). Based on the approach used in a previous report,[18] the layered structure, the thickness of cartilage and perichondral tissue and power Doppler signal (PDS) patterns were evaluated, and these findings were retrospectively reviewed.

Next, we retrospectively examined the relationship between clinical symptoms, ultrasonographic findings of auricular and nasal cartilage and serologic inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR] and serum amyloid A) before and after treatment with methotrexate and prednisolone (PSL) for RP. We used the Relapsing Polychondritis Disease Activity Index proposed by Arnaud et al as the clinical remission standard.[19]

Furthermore, the ultrasonographic findings of the auricular and nasal cartilage of patients with RP (n = 6) were compared with those of patients with repeat trauma (n = 6), for which the deformation of the auricles is similar to that in RP, auricular cellulitis including infectious chondritis (n = 6), for which the finding of swollen auricles is similar to that in RP and healthy controls (n = 6). These control groups were age- and sex-matched groups to the RP patients.

This study was approved by the Ethics Committee of Kochi Medical School Hospital (approval #28-50) and conducted in accordance with the Declaration of Helsinki. All clinical information was obtained after patients provided written informed consent. Age, CRP level and ESR are presented as mean ±SD calculated using GraphPad Prism version 4.00c for Macintosh (GraphPad Software). We used the Chi-square test for comparison of variables between 2 groups or one-way analysis of variance. Results were considered significant at $P < .05$.

3 | RESULTS

3.1 | Background of enrolled patients and healthy controls

Of all patients with RP who were diagnosed in our hospital between 2014 and 2019, 6 patients with RP who were evaluated for cartilage lesions using ultrasonography were enrolled in this study. Of these 6 patients, 3 were men and 3 were women, with a mean age of 56 ± 4 years. All 6 patients had auricular chondritis. Other complications included nasal chondritis in 1 patient, tracheal chondritis in 1 patient, optic perineuritis in 1 patient and uveitis in 2 patients. Mean CRP level and ESR in 6 patients with RP were 6.2 ± 3.5 mg/dL and 82 ± 43 mm/h, respectively. The age- and sex-matched controls to the RP group consisted of 6 patients with chronic trauma (mean age,

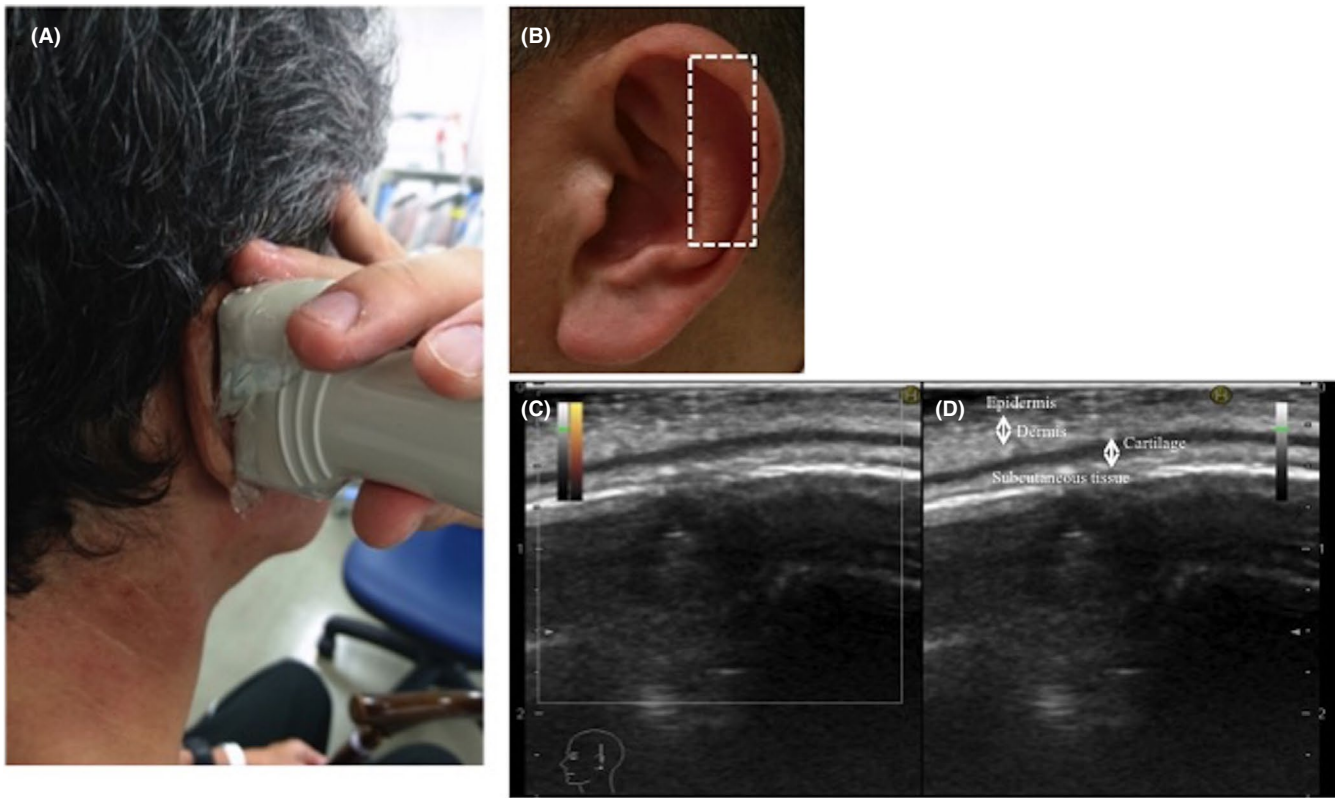

FIGURE 1 Ultrasonographic findings of normal auricles in healthy controls. Noblus (Hitachi) was used as the ultrasound system for evaluation of cartilage lesions, and the 12-MHz linear-type probe was used (A). The auricle in a healthy control showed 4 layers of epidermis, dermis, auricular cartilage and subcutaneous tissue in order from the surface layer (B and D). The auricular cartilage was depicted as a layer of low-echoic lesion without changes of the soft-tissue around the cartilage, and power Doppler signal enhancement was not observed in cartilage or surrounding soft tissue by power Doppler imaging (C and D)

48 ± 3 years; 4 men, 2 women), 2 patients with auricular cellulitis (mean age 53 ± 5 years; 1 man, 1 woman) and 6 healthy volunteers (mean age 45 ± 7 years; 4 men, 2 women).

3.2 | Ultrasonographic findings of normal auricles and nose in healthy controls

The ultrasonographic findings of the auricles in the healthy control group were epidermis, dermis, auricular cartilage and subcutaneous tissue from the surface layer. The auricular cartilage was depicted as a layer of low-echoic lesion, and no change was observed in the soft tissue around the cartilage. Additionally, PDS enhancement was not observed in the cartilage or surrounding soft tissue by power Doppler imaging (Figure 1B-D). Similar findings were also shown in the normal nose (Figure S1B).

3.3 | Ultrasonographic findings of auricular chondritis on diagnosis or before treatment of RP patients

In all 6 patients diagnosed with RP, active auricular chondritis with swelling/redness of the auricle was observed on clinical examination. Figure 2A presents a representative gross photograph. Ultrasonographic findings at the same site before the start of treatment revealed hypoechoic soft-tissue swelling around the auricular cartilage accompanied by PDS enhancement at the same site (Figure 2B,C). Additionally, FDG-PET/CT and MRI revealed increased FDG uptake (Figure 2D,E) and high-intensity lesions, respectively, which were consistent with abnormal findings on ultrasonography. Furthermore, pathologic findings of biopsy from auricular cartilage included perichondral inflammatory cell infiltration and capillary neovascularization as well as cartilage degeneration (Figure 2F,G).

3.4 | Ultrasonographic findings of nasal chondritis in the diagnosis or before treatment of a RP patient

In 1 patient diagnosed with RP, active chondritis with swelling of the nose was observed on clinical examination. Figure S2A presents a representative gross photograph. Ultrasonographic findings at the same site before the start of treatment revealed soft-tissue swelling around the nasal cartilage accompanied by PDS enhancement at the same site (Figure S2B). In addition, FDG-PET/CT showed increased FDG uptake (Figure S2C), which was consistent with abnormal findings on ultrasonography. Furthermore, pathological findings of biopsy from nasal cartilage included perichondral inflammatory

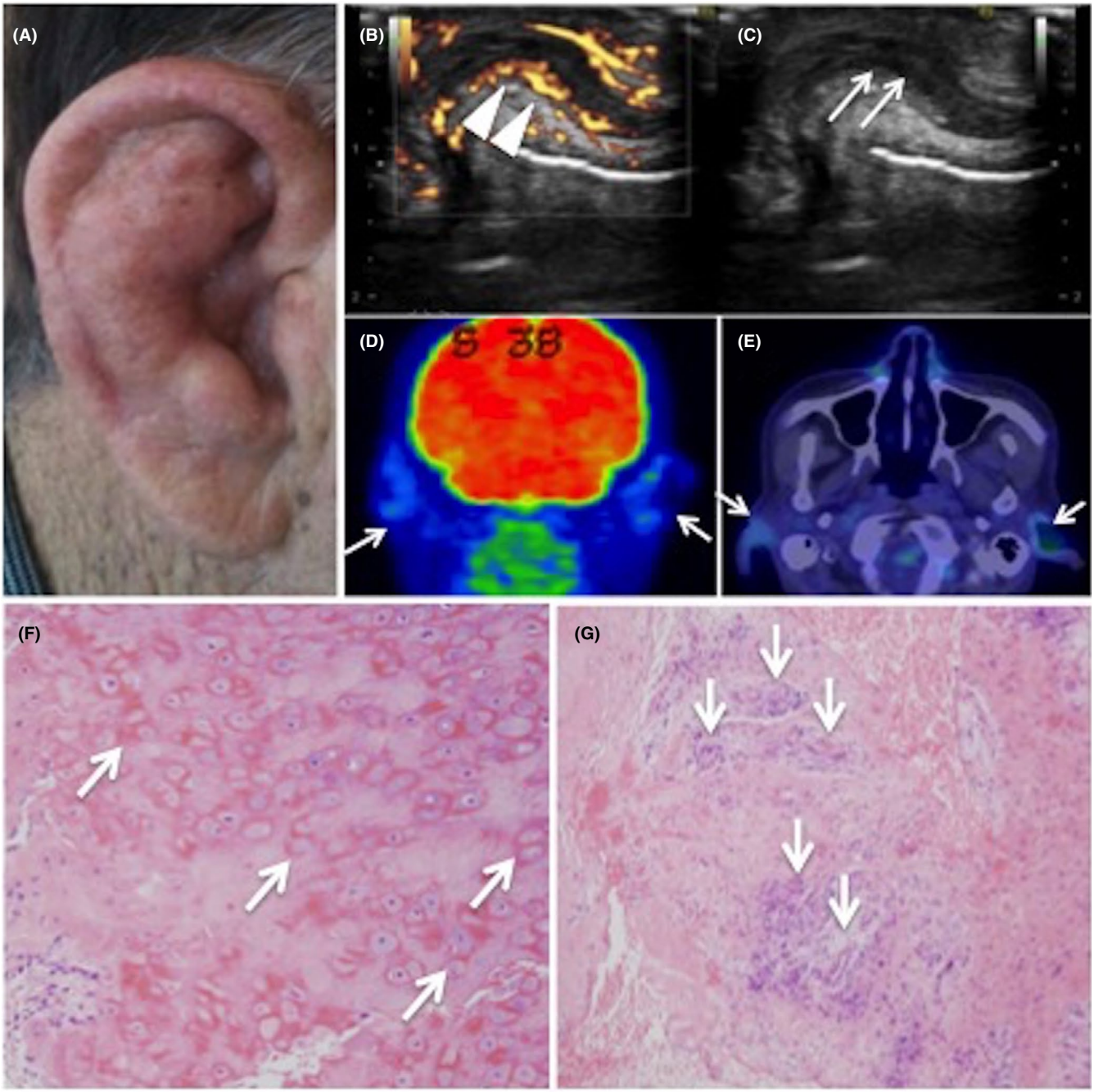

FIGURE 2 Ultrasonographic findings of auricular chondritis in the diagnosis of relapsing polychondritis. A representative gross photograph is shown (A). Ultrasound findings at the same site before the start of treatment revealed hypoechoic soft-tissue swelling (arrows) around the auricular cartilage accompanied by power Doppler signal enhancement (arrowheads) at the same site (B and C). Fluorodeoxyglucose (FDG)–positron emission tomography/computed tomography revealed increased FDG uptake (D and E, arrows). Pathologic findings of biopsy from auricular cartilage revealed cartilage degeneration (F, arrows) and perichondral inflammatory cell infiltration and capillary neovascularization (G, arrows)

cell infiltration and capillary neovascularization as well as cartilage degeneration (Figure S2D).

3.5 | Changes in ultrasonographic findings before and after treatment in RP patients

Four of the 6 patients treated with combination therapy consisting of PSL and methotrexate showed improvement in macroscopic and ultrasonographic auricular swelling in accordance with improvement of serologic inflammatory markers (Figure 3). Similar change before and after treatment was also shown in 1 RP patient with nasal chondritis (Figure S3). In contrast, on imaging evaluation, 1 patient had persistent soft-tissue swelling and enhancement of PDS on ultrasonography, despite optimal clinical response that was already achieved within 4 weeks. This patient required continued treatment for an additional 4 weeks to achieve ultrasonographic remission (Figure 4). Also, 1 RP patient with persistent PDS relapsed during

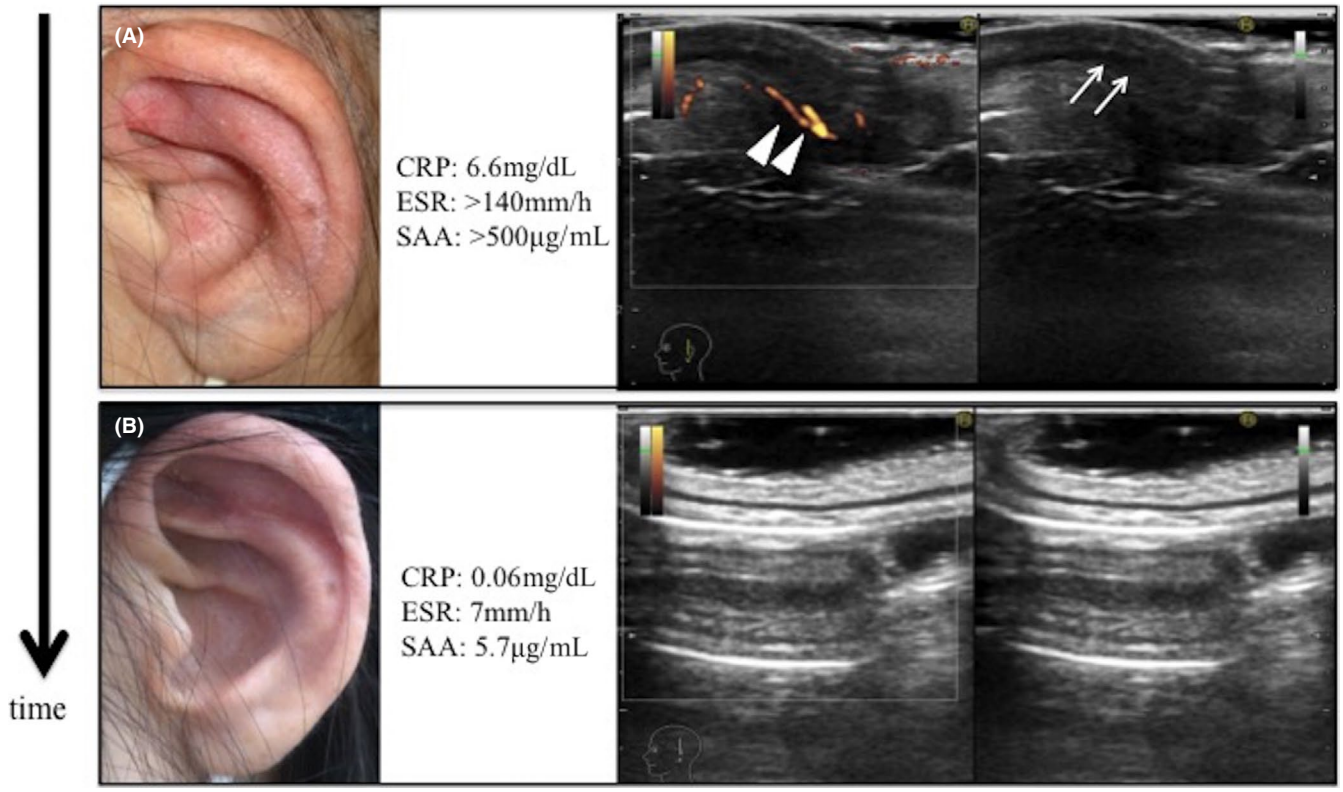

FIGURE 3 Changes in ultrasonographic findings before and after treatment in relapsing polychondritis. Most of the 6 patients showed improvement after treatment of macroscopic auricular swelling and redness and serologic inflammatory markers (B), compared with before treatment (A). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A

PSL tapering after 2 months of achievement of clinical remission but subsequently achieved clinical and ultrasonographic remission again with an increased dose of PSL for 1 month (Figure 5).

3.6 | Ultrasonographic findings in patients with repeat trauma to the pinna

The auricles of patients with repeated physical stimuli, such as judo and rugby, and repeated trauma were macroscopically similar to those of RP patients (Figure S4A). Ultrasonography showed swelling of the soft tissue around the auricular cartilage and fluid accumulation in the subcutaneous tissue; however, no enhancement of PDS was observed (Figure S4B,C).

3.7 | Ultrasonographic findings in patients with cellulitis of the pinna

The auricles of 6 patients with cellulitis including infectious chondritis were assessed in our hospital, and auricular cellulitis was macroscopically similar to those of the RP patients (Figure S5A). We observed the swelling of soft tissue at the infected site and PDS enhancement in the superficial to deep layer on ultrasonography in a patient who developed auricular cellulitis (Figure S5B,C).

3.8 | Comparison of ultrasonographic findings of auricular cartilage between patients with RP, repeat trauma and cellulitis and healthy controls

In the RP and repeat trauma groups, we observed enlarged low-echoic lesions, reflecting soft-tissue swelling around the auricular cartilage. We observed fluid accumulation in the subcutaneous tissue in patients with chronic trauma, although this finding was not observed in patients with RP or in healthy controls ($P < .05$), as shown in Table 1. Also, PDS enhancement in the enlarged soft tissue around the auricular cartilage was observed in the RP group, but not in chronic trauma patients or healthy controls ($P < .05$), as shown in Table 1. Distribution patterns of PDS were obviously different between the RP and auricular cellulitis groups (Table 1).

4 | DISCUSSION

Recently, ultrasonography of the joints and entheses has been widely used in the diagnosis and evaluation of disease activity of rheumatoid arthritis (RA) and psoriatic arthritis (PsA).[20–25] Thus, although ultrasonography is widely used clinically in the field of rheumatology, either no or poor consensus exists regarding its usefulness for assessment of chondritis in RP.[26,27] In this study, we retrospectively reviewed changes of auricular and nasal chondritis in 6 patients with

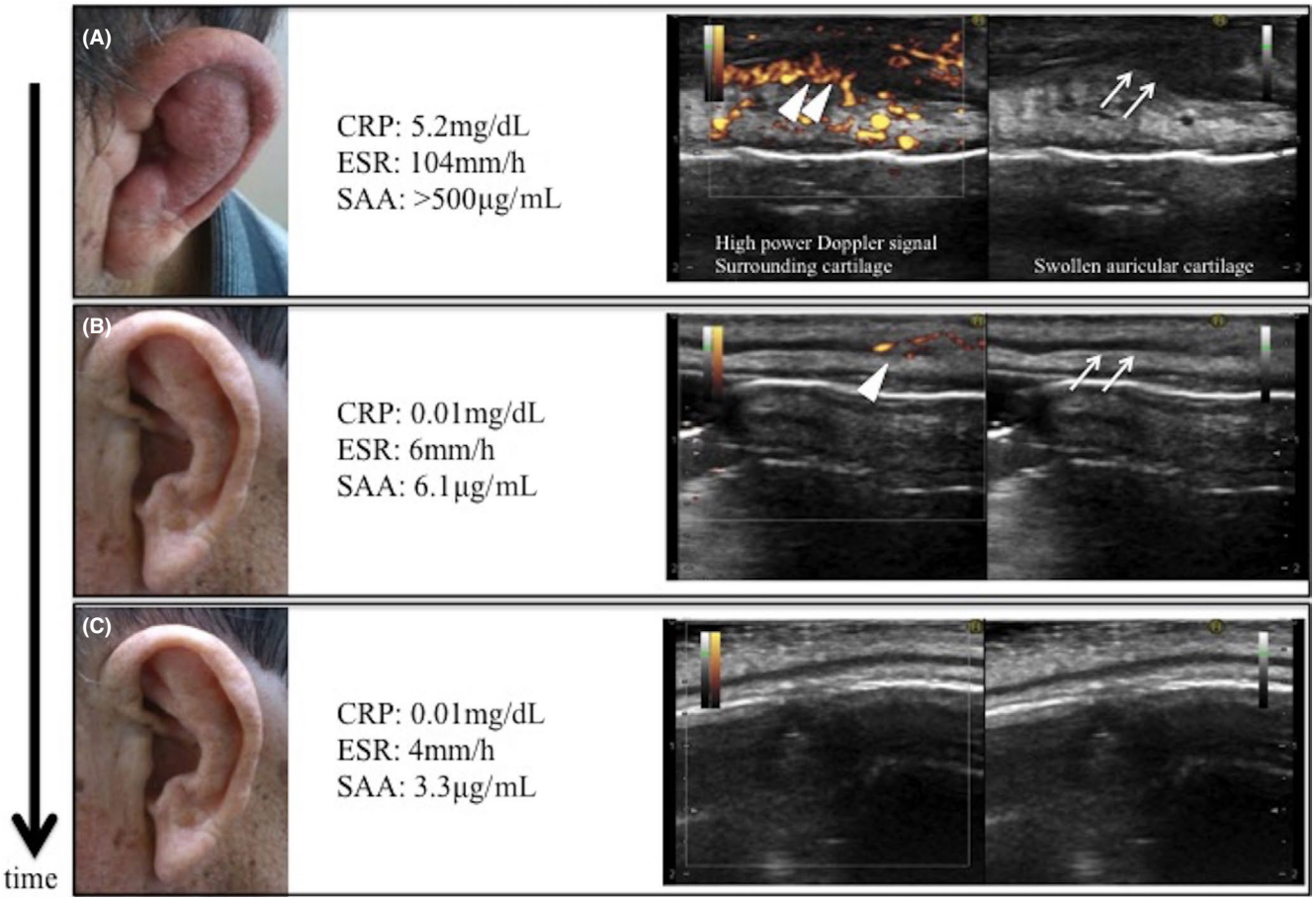

FIGURE 4 Changes in ultrasonographic findings before and after treatment in relapsing polychondritis. Soft-tissue swelling and PDS enhancement were revealed before treatment (A). Soft-tissue swelling and PDS enhancement on ultrasonography persisted, even when macroscopic findings were improved (B). Later, the imaging improvement was delayed by continuation of treatment (C). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PDS, power Doppler signal; SAA, serum amyloid A

RP by ultrasonography before and after treatment to evaluate the usefulness of ultrasonography. This study suggested that the ultrasonographic finding of active auricular chondritis in RP revealed perichondral soft-tissue swelling and PDS enhancement; therefore, ultrasonography could help clinicians diagnose the disease, evaluate disease activity and consider the therapeutic strategy, especially drug tapering, in patients with RP.

The first major point is that ultrasonography may be useful for the evaluation of auricular chondritis in the diagnosis of patients with RP. Based on the present study findings, active inflammation in the auricular cartilage of RP patients was visualized by ultrasonography as hypoechoic swelling of the perichondral soft tissues and PDS enhancement. Ultrasonographic examination of the auricle in healthy controls demonstrated that the auricle comprised a 4-layer structure, and the auricular cartilage was described as a layer of low-echoic lesion. In patients who experienced repeat auricular trauma, ultrasonographic finding revealed an indistinct layer structure along with perichondral soft-tissue swelling and fluid retention without PDS enhancement. These results from healthy controls and patients with repeat trauma were consistent with those of a previous report;[18] therefore, we suggest that perichondral soft-tissue swelling with PDS enhancement indicates active inflammation of auricular cartilage. In fact, in RA and PsA, PDS is enhanced at sites exhibiting active synovitis, tenosynovitis, enthesitis and other signs, which are findings that reflect increased blood flow due to abnormal vascularization and vasodilation associated with inflammation. Essentially, cartilage is a poorly vascularized tissue. The progression of inflammation leads to the infiltration of inflammatory cells into the cartilage and the surrounding tissue. In terms of pathologic findings of auricular lesions in RP patients, previous reports on biopsies from cartilage performed in RP patients revealed the infiltration of inflammatory cells, such as lymphocytes, plasma cells and macrophages into the perichondral tissues, capillary neogenesis contributing to microcirculation enhancement and cartilage degeneration.[27,28] Neovascularization also plays an important role in the maintenance and progression of inflammation in many rheumatic diseases, including RA and spondyloarthritis.[29] These findings were also consistent with the pathologic and ultrasound findings in this study. One might ask whether ultrasonography differentiates RP from the conditions where the infection has reached the cartilage (ie infectious chondritis). Considering the results of this study (Table 1), RP could be differentiated from cellulitis including

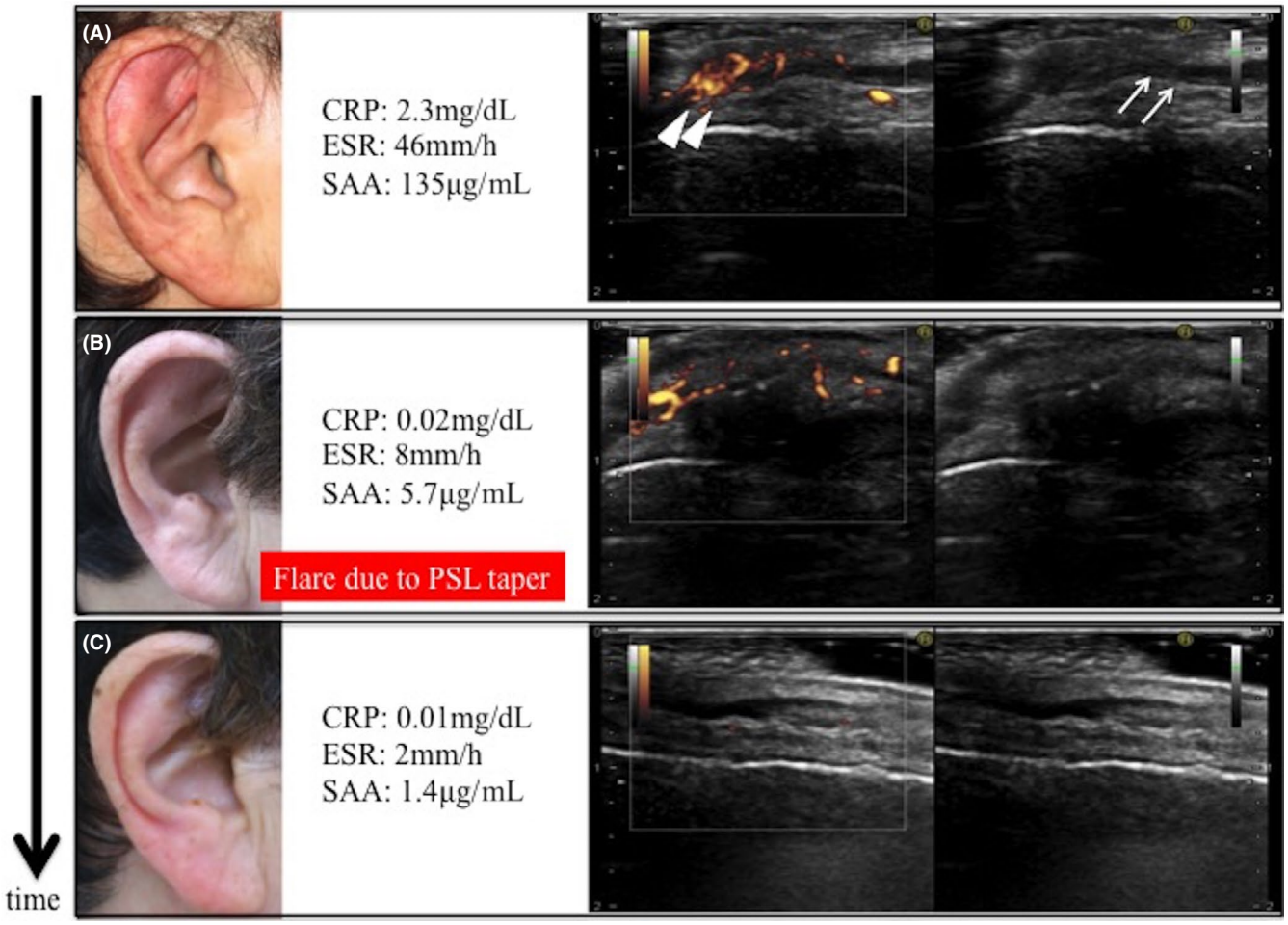

FIGURE 5 Changes in ultrasonographic findings before and after treatment in relapsing polychondritis. Soft-tissue swelling and PDS enhancement were revealed before treatment (A). One patient with persistent PDS relapsed during PSL tapering (B), but the patient achieved clinical remission again with a dose increase of PSL, and PDS also disappeared (C). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PDS, power Doppler signal; PSL, prednisolone; SAA, serum amyloid A

TABLE 1 Comparison of auricular ultrasonographic findings among the healthy controls and the repeat trauma, auricular cellulitis and RP groups

Finding	Healthy controls (n = 6)	Repeat trauma group (n = 6)	Auricular cellulitis group (n = 6)	RP group (n = 6)
Auricular perichondral soft-tissue swelling	0/6 (0%)	6/6 (100%) Moderate to severe	6/6 (100%) Mild	6/6 (100%) Moderate to severe
Subperichondral effusion	0/6 (0%)	4/6 (66.7%)	0/6 (0%)*	0/6 (0%)*
Increased PDS	0/6 (0%)	0/6 (0%)	6/6 (100%)*,**	6/6 (100%)*,**
Distribution of PDS	N/A	N/A	Superficial to deep layer	Perichondral layer

Abbreviations: N/A, not available; PDS, power Doppler signal; RP, relapsing polychondritis.

*$P < .05$ vs repeat trauma group.; **$P < .05$ vs healthy controls and repeat trauma group.

infectious chondritis by the different distribution patterns of PDS. Furthermore, ultrasonographic findings of infectious chondritis showed that cartilage increased in echogenicity and could appear beaded in the previous report,[18] indicating the dissimilarity between RP and infectious chondritis; thus, ultrasonography of the auricle can identify active inflammatory findings specific to RP and be useful for the diagnosis of RP with auricular and nasal chondritis.

The second major point of this study is that ultrasonographic findings in auricular and nasal lesions may reflect disease activity of RP. There are no serologically specific and easily measurable markers for RP; therefore, it is difficult to identify disease activity of RP.[7] Although some previous studies reported the clinical implications of imaging tests such as contrast-enhanced CT, MRI, FDG-PET/CT and bone scintigraphy for assessment of disease activity,[9–16] performing

these imaging tests frequently is unrealistic without careful consideration of cost, convenience, invasiveness and radiation exposure. In tracheal chondritis—one of the fatal complications in RP—it has been reported that endobronchial ultrasonography is useful for monitoring disease activity.[30–32] Swelling of the submucosal and cartilage layer and improvement in swelling is observed when the disease activity is high and low, respectively. In contrast, because bronchoscopy itself is highly invasive and may cause respiratory failure, it is critical for clinicians to be careful about its indication. Therefore, one of the clinical issues in RP is to establish an imaging method that can evaluate disease activity and be performed more noninvasively and easily. In this study, inflammatory changes such as increased blood flow and soft-tissue swelling by auricular ultrasonography disappeared in patients with clinical remission of RP who had immunosuppressive therapy, and the results were consistent with those in healthy controls in terms of imaging findings, suggesting that ultrasonography could also be useful for evaluating the therapeutic effect of auricular chondritis and monitoring disease activity in RP patients.

Clinicians may justifiably question whether ultrasonographic findings should always influence the decision to step down treatment in RP. Currently, a treat-to-target strategy has been introduced as a treatment strategy for RA and PsA, resulting in significant improvement in joint prognosis.[33] However, it has been reported that if imaging evidence of inflammation persists despite clinical remission, then the visualized inflammation may be associated with a subsequent flare or radiographic progression.[34,35] It has also been reported that maintenance of remission on imaging may be useful for the subsequent reduction of the flare rate, improvement of functional prognosis, the step-down strategy of treatment and other considerations.[36,37] Likewise, in RP, it was also reported that imaging tests including CT and MRI correlated better with clinical assessment of therapeutic response than with nonspecific inflammatory laboratory markers.[9] In this study, RP flare was observed during the tapering of PSL in patients with auricular chondritis with residual PDS enhancement, despite clinical remission. In contrast, patients who could maintain the resolution of PDS also maintained remission without flare, and 1 patient who experienced flare did not demonstrate flare after achieving ultrasonographic remission. These results suggest that ultrasonography is more useful for predicting subsequent flare in RP, similar to prediction in RA; thus, when PDS enhancement on auricular ultrasonography persists, we should taper the steroid more slowly to prevent flare and to target ultrasonographic remission.

The limitation of this study is that it is a single-center, retrospective study with a small sample size. Because the technique of ultrasonography of the auricle has not yet been established, further large-scale prospective studies are needed.

In conclusion, ultrasonography may be useful for diagnosis of RP, monitoring disease activity and determining therapeutic strategies, especially by focusing on the presence or absence of PDS enhancement in RP with auricular chondritis. Because RP is a rare disease, it is hoped that more data for additional cases can be accumulated and examined in the future and that ultrasonography will be established as an inexpensive, noninvasive, radiation-free modality for the diagnosis of RP and for monitoring of disease activity in RP.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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