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# Crico-thyroid perichondritis leading to sore throat in patients with active adult-onset Still's disease

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*Ann Rheum Dis* 2007;**66**:1264–1266. doi: 10.1136/ard.2006.065342

A review of 341 adult-onset Still's disease (AOSD) patients noted that 69% of all reported cases[1] and 84% (69/82) of our series[2] displayed sore throat early in the disease course. Despite the presence of severe sore throat, physical examinations showed normal findings or only mild pharyngeal infection, and imaging studies (including computed tomography (CT) scans) of the neck were negative.[1–4] The lesions responsible for sore throat in active AOSD patients have not yet been explored.

We performed magnetic resonance imaging (MRI) of the larynx[5] in 6 active AOSD patients (3 females and 3 males; mean age 33.5 years; table 1) presenting with sore throat and fulfilling the Yamaguchi criteria.[6] Our aim was to identify the lesions responsible for sore throat in AOSD patients. Throat swabs for bacterial cultures were negative and serological tests for viruses were non-diagnostic in all AOSD patients. Serum levels of C-reactive protein (CRP) were elevated in all of our active AOSD patients. Three AOSD patients were available for MRI examination both at the active phase when presenting with sore throat, and at the remission phase (defined as the absence of systemic manifestation and sore throat within 6 months of effective therapy). The Ethics Committee of Clinical Research, Taichung Veterans General Hospital, approved this study protocol.

A brief summary of clinical and MRI findings of our 6 AOSD patients during sore throat was shown in table 1. The $T_1$-weighted images showed increased thickness of soft tissue near the crico-thyroid cartilage (case 1 and fig 1A), and the post-contrast $T_1$-weighted images demonstrated marked enhancement at the perichondral tissue (fig 1B). In an AOSD patient presenting with odynophagia, the post-contrast T1-weighted image showed marked enhancement at the soft tissue near cricoid-thyroid cartilages and the pharynx (case 5 and fig 1C). Gallium-67 scintography showed an increased uptake intensity at the corresponding region (fig 1D). In a patient who had redness of the laryngeal mucosa shown by indirect laryngoscope, a $T_2$-weighted image illustrated increased signal intensity at the soft tissue surrounding the vocal cord (case 6). During a longitudinal

**Abbreviations:** AOSD, adult-onset Still's disease; CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging

**Table 1** Summary of clinical and MRI findings of 6 patients with adult-onset Still's disease during sore throat

| Case | Age/Sex | Clinical features of sore throat | Findings of indirect laryngoscopic examination | CRP levels (mg/dl) | MRI findings | |
|---|---|---|---|---|---|---|
| | | | | | $T_2$-weighted | Post-contrast $T_1$ |
| 1 | 28/F | Left-sided sore throat | Normal | 4.2 | Increased signal intensity at left-sided crico-thyroid cartilage | Marked enhancement |
| 2 | 34/F | Sore throat | Normal | 1.6 | Increased signal intensity at pre-epiglottic area | Mild enhancement |
| 3 | 27/M | Sore throat | Normal | 5.7 | Increased signal intensity along bilateral thyroid cartilages | Marked enhancement |
| 4 | 35/M | Sore throat | Normal | 6.6 | Increased signal intensity near cricoid cartilage | Mild enhancement |
| 5 | 25/F | Severe sore throat with odynophagia | Redness of pharyngeal mucosa | 10.7 | Increased signal intensity at crico-thyroid cartilages and pharynx | Marked enhancement |
| 6 | 52/M | Severe sore throat | Redness of laryngeal mucosa | 11.3 | Increased thickness with high signal intensity at the tissue surrounding vocal cord | Marked enhancement |

M, male; F, female; CRP, C-reactive protein; MRI, magnetic resonance imaging.

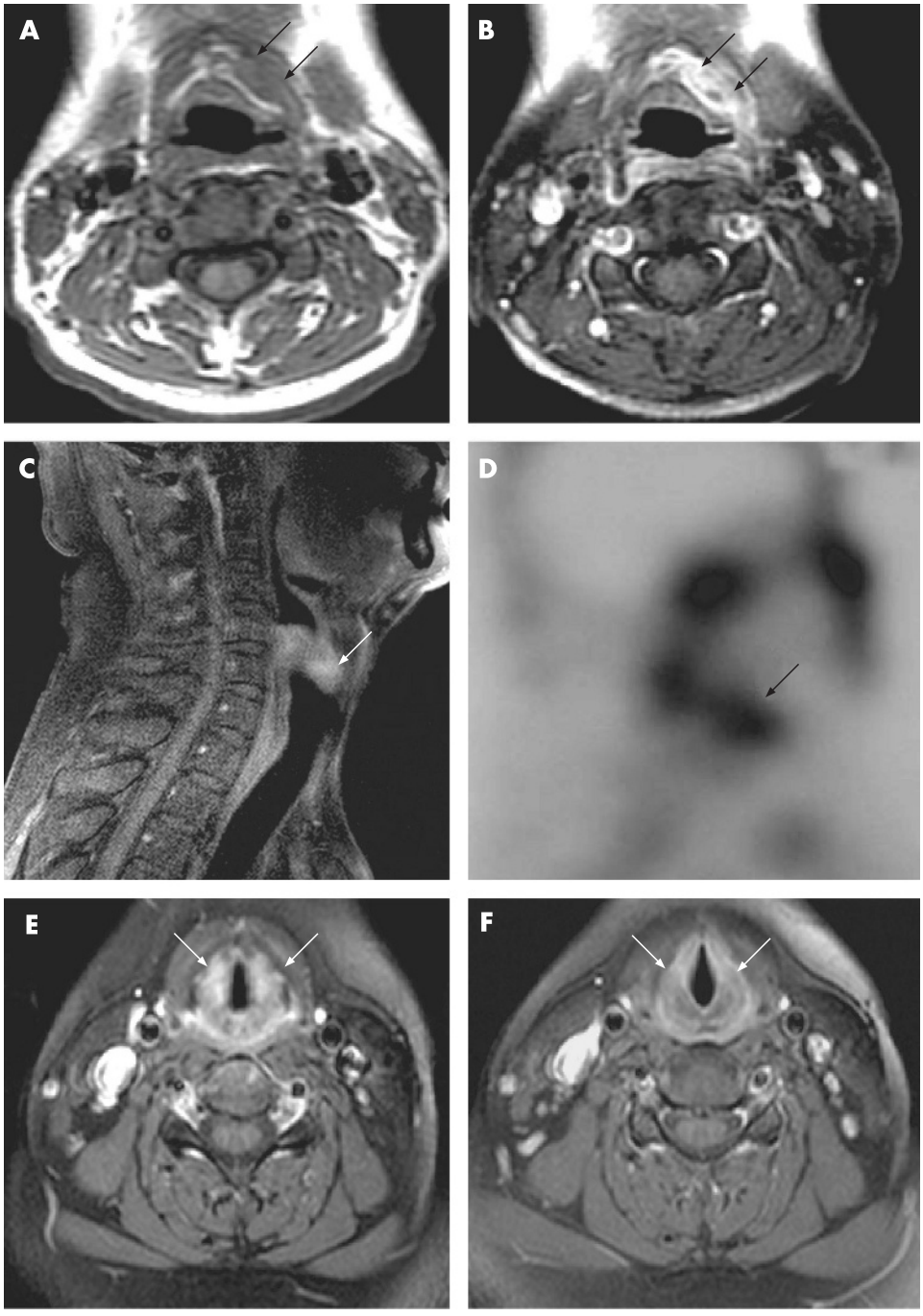


**Figure 1** MRI findings of the larynx in case 1 presented with left-sided sore throat lasting for 2 weeks. (A) Axial, $T_1$-weighted image shows increased thickness of soft tissue near the left half of the thyroid cartilage (arrows). (B) Post-contrast $T_1$-weighted image demonstrates marked enhancement at the same region (arrows). In case 5, presenting with odynophagia, the sagittal plane of the post-contrast T1-weighted image (C) shows an increase in thickness with marked enhancement at the soft tissue near the cricoid-thyroid cartilage and the pharynx (arrow). In this patient, Gallium-67 scintography (D) shows increased uptake intensity at the corresponding region (arrow). A change in MRI findings after effective therapy was observed in case 6. The axial plane of the post-contrast T1-weighted image shows increased thickness with marked enhancement at the soft tissue near the vocal cord in the active phase (E, arrows), and it resumed to normal appearance at the same area (F, arrows) after 5 months' therapy in this patient.

follow-up, the inflammatory signs shown by MRI markedly subsided (fig 1E, 1F), paralleling clinical remission and the decrease in CRP (mean ± SD, 6.5 ± 4.8 mg/dl vs 0.1 ± 0.0 mg/dl).

## DISCUSSION

There are no further image studies concerning the cause of sore throat in AOSD patients following negative findings of CT scans.[1] We demonstrated high signal intensity with contrast enhancement over soft tissue surrounding crico-thyroid cartilage and/or vocal cords in active AOSD patients presenting with sore throat. Perichondritis of crico-thyroid cartilage and/or corditis may explain the sore throat, and the close proximity between the involved area and pharyngeal constrictors may lead to odynophagia. The evidence of inflammation was supported by an increase in the uptake intensity of Gallium-67 citrate, which has a high affinity for inflammatory lesions.[7] MRI changes of crico-thyroid cartilage parallel clinical remission and the decrease in serum CRP levels in AOSD patients. Our results suggest that crico-thyroid perichondritis, demonstrated by MRI, may precipitate the pathogenesis of sore throat in AOSD.

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Competing interests: None declared.

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Accepted 19 February 2007

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# The low-penetrance R92Q mutation of the tumour necrosis factor superfamily 1A gene is neither a major risk factor for Wegener's granulomatosis nor multiple sclerosis

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*Ann Rheum Dis* 2007;**66**:1266–1267. doi: 10.1136/ard.2006.065987

Inherited autosomal-dominant mutations in the tumour necrosis factor receptor superfamily 1A (*TNFRSF1A*) gene encoding the tumour necrosis factor receptor p55 (TNF-R1) are the cause of an auto-inflammatory syndrome that is characterized by periodic fever attacks, aseptic peritonitis, arthritis, meningitis, conjunctivitis, pleuritis and skin rash (OMIM #142680). The most common TNFR-associated periodic syndrome (TRAPS)-like disease that is associated with a R92Q mutation, however, occurs sporadically, with later onset (median 23 years vs 7 years with other mutations) and a milder and often oligosymptomatic course.[1 2] Intriguingly, carriers of the R92Q allele bear a slightly increased risk for some other diseases, such as myocardial infarction,[3] increased carotid intima-media thickness,[3] thrombotic complications in Behcet's disease[4] and early synovitis.[1]

Due to the low uncertain frequency of the R92Q allele in various ethnic populations (0.5–1%), the available data about multiple sclerosis (MS) patients[5 6] do not exclude a possible risk of R92Q mutations being present. Recent case reports on small-vessel vasculitis in patients with *TNFRSF1A* mutations (R92Q, T50M)[7] and inflammatory manifestations of *TNFRSF1A* mutations in the central nervous system[8] prompted us to investigate a possible mutual relationship between R92Q mutations, MS and Wegener's granulomatosis (WG) in the German population.

A total of 446 MS, 268 WG and 265 control cases (table 1) were analysed for the presence of the R92Q allele by sequencing and *Nci*I digestion of a PCR-amplified segment (detailed information on request). Apart from the R92Q heterozygous mutation, we have not found other sequence variations in these patients that affect the extracellular domain of the TNF-R1 receptor. Dinucleotide repeat length analysis performed in 15 R92Q$^+$ patients from the MS and WG cohorts confirmed the sharing of an identical repeat length haplotype.[9]

The odds ratios that we obtained (0.64 for MS and 0.91 for WG) do not indicate a significant association of the R92Q allele with these diseases. Although the confidence intervals are relatively large, the data permit us to exclude a more than 2-fold risk of the R92Q allele in cases of WG and a more than 1.3-fold risk for MS cases. As both the frequency and the remaining

**Abbreviations:** MS, multiple sclerosis; TNFRSF1A, tumour necrosis factor receptor superfamily 1A; TRAPS, TNFR-associated periodic syndrome; WG, Wegener's granulomatosis

**Table 1** R92Q frequencies in MS and WG patients and in healthy controls

| | R92Q+ | R92Q− | r(R92Q)* | OR† | p‡ | CI§ |
|---|---|---|---|---|---|---|
| MS | 13 | 446 | 2.9 | 0.64 | 0.38 | 0.32–1.26 |
| WG | 11 | 268 | 4.1 | 0.91 | 0.99 | 0.39–2.09 |
| HC¶ | 12 | 265 | 4.5 | | | |

*Carrier frequency; †OR, odds ratio; ‡Two-tailed p value using the chi-square test with Yates correction (http://graphpad.com/quickcalcs/contingency2.cfm); §CI, confidence interval at the 95% level of confidence. OR and CI were determined via the web-based calculator: http://www.hutchon.net/ConfidORselect.htm; ¶Healthy controls (blood donors).