

# Extraintestinal Crohn's Disease Mimicking Autoimmune Inner Ear Disease: A Histopathological Approach

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## Key Words

Hearing loss · Immunohistochemistry · Inner ear neurobiology · Inner ear therapy · Vertigo · Vestibular diseases

## Abstract

Patients with autoimmune inner ear disease develop rapidly progressive sensorineural hearing loss over a period of several weeks or months, often accompanied by vestibular loss. This disease can occur as a distinct clinical entity or in association with an underlying autoimmune disorder. Treatment comprises immunosuppression by corticosteroids, cytostatic drugs or tumor necrosis factor- $\alpha$  antagonists. We report histopathological and immunohistochemical findings of the inner ear of a patient with a granulomatous inner ear disease suffering from Crohn's disease that was nonresponsive to treatment and who underwent surgery for bilateral cochlear implants.

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## Case Report

A 27-year-old teacher was admitted to our ENT outpatient department because of repetitive attacks of rotary vertigo lasting about 1 day and repetitive sudden sensorineural hearing loss

(SNHL). Ulcerative colitis had been diagnosed 9 months previously (2006) and the patient was on oral prednisone (20 mg/day) and azathioprine (150 mg/day). Tapering prednisone had been tried several times without success as bowel symptoms worsened. Immunomodulatory therapy by infliximab was stopped because of side effects like itching, slight erythema on both upper arms due to scratching and maculopapulous partly pustular rash on the face, chest and back. No other side effects had been reported. Subsequently certolizumab was initiated with no beneficial effect on the patient's hearing capacity and no adverse events.

His family medical history revealed neither autoimmune disease nor hearing loss. A normal ophthalmologic examination ruled out Cogan's syndrome in differential diagnosis. In June 2008 the patient developed aphthous lesions on the oral mucosa and granulomatous cheilitis. This and the finding of fistulas and abscesses of the colon led to a revision of the diagnosis to Crohn's disease.

The first vertigo attack was noticed about 6 weeks and the first signs of hearing loss about 3 weeks before we saw the patient. Hearing loss first occurred on the right ear with tinnitus. The patient had been treated previously in a private practice outside Switzerland with antibiotics for otitis media, although there was no pain or feeling of pressure in the ear. An audiogram or other reports from this doctor were not available. The first audiogram in our clinic showed a bilateral SNHL of 50–55 dB at 0.125–2 kHz, 90–100 dB at 3–8 kHz. On the left there was also SNHL of 20–35 dB between 0.125 and 4 kHz and 45/35 dB at 6/8 kHz. At 12 kHz no tone was heard bilaterally. An MRI performed about half a year after the onset of symptoms showed a clear enhancement of contrast medium (gadolinium) in the left labyrinth. Four months lat-

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er there was still significant contrast medium enhancement on the left and a possible enhancement in the semicircular canals on the right as well (fig. 1).

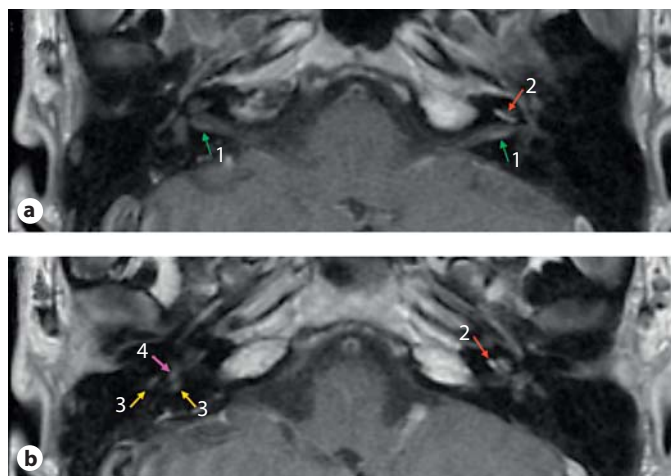
The pure-tone average at 0.5, 1 and 4 kHz was 26.25 dB on the left and 62.5 dB on the right ear. At that time the subjective visual vertical was tilted 2° to the left (pathological >2°) and the caloric response was only 2°/s with warm water (44°C) on the left and cold water (30°C) on the right. He had a right beating spontaneous nystagmus of 2°/s when looking to the right and complete visual suppression. There was also a head shaking nystagmus to the right of 3°/s. Smooth pursuit and saccades were normal. There were no other neurological symptoms or signs. Vestibular evoked myogenic potentials were reproducible on the right with clearly prolonged latencies ( $P_{13}$  at 22.0 and 22.9 ms), but could not be evoked on the left, indicating a loss of saccular function on the left and a lesion, possibly in the vestibular nerve, on the left. Half a year later there was no spontaneous, gaze-evoked or head shaking nystagmus. Vestibular tests revealed complete bilateral loss: a caloric nystagmus of 2° on cold water irrigation on the left and the head impulse test showed gain values for all semicircular canal planes between 0.06 and 0.25. Two transtympanic injections of about 0.5 ml dexamethasone (4 mg/ml) in both ears had a short, transient effect on hearing loss. Hearing was fluctuating with losses every 3–7 days. Four-tone pure-tone average increased from 62.5/26.25 dB (right/left) on August 28th 2008 to 113.7 dB on the right and complete deafness on the left on May 28th 2009.

In summary, after having several episodes of sudden SNHL on both sides, the patient developed complete bilateral hearing and vestibular loss in less than 9 months. Summarizing clinical symptoms an autoimmune inner ear disease (AIED) was postulated.

68-kD Western blot, previously used in AIED [Gottschlich et al., 1995; Moscicki et al., 1994], was not performed because sensitivity and specificity are controversial. Laboratory tests revealed normal values for C-reactive protein on repeated analysis. Antiviral IgG antibodies against herpes simplex virus 1 and varicella zoster virus were positive with negative IgM, implying past infection. IgG against herpes simplex virus 2, *Borrelia burgdorferi* and *Treponema pallidum* were completely negative. Total serum IgG was borderline (16.2 g/l; normal value <16.0 g/l). Antinuclear antibodies and anti-native DNA antibodies were negative, whereas anti-neutrophil cytoplasmic antibodies were positive at low titer (1:40). Further specification showed neither classical reactivity to proteinase 3 nor atypical reactivity to myeloperoxidase.

Furthermore, testing for antiphospholipid antibodies, anti-cardiolipin and anti- $\beta_2$ -glycoprotein 1 revealed negative results for all immunoglobulin classes as well as antimitochondrial and anti-smooth muscle antibodies. Lumbar puncture was also performed with normal values for glucose, lactate and protein and <1 cell/ $\mu$ l.

After oral and intratympanic treatment with dexamethasone had been unsuccessful, we started treatment with intravenous infliximab (Remicade, 5 mg/kg). Although there was a slight improvement in gastrointestinal symptoms, there was no significant effect on hearing and an MRI showed persistent contrast medium enhancement in the labyrinths. As the above-mentioned adverse events occurred the regimen was changed to certolizimab (Cimzia, 400 mg subcutaneously), which caused no side effects but failed to improve or stabilize hearing. Finally the patient received cochlear implants (CIs), first on the left and 2 months later on the right side. There was some granulomatous tissue in the inner ear



**Fig. 1.** T<sub>1</sub>-weighted MRI with gadolinium showing slight gadolinium enhancement in the vestibular nerve bilaterally (1) and in the left cochlea (2) (a), and in the left cochlea (2), the right horizontal semicircular canal (3), and in the right vestibulum (4) (b).

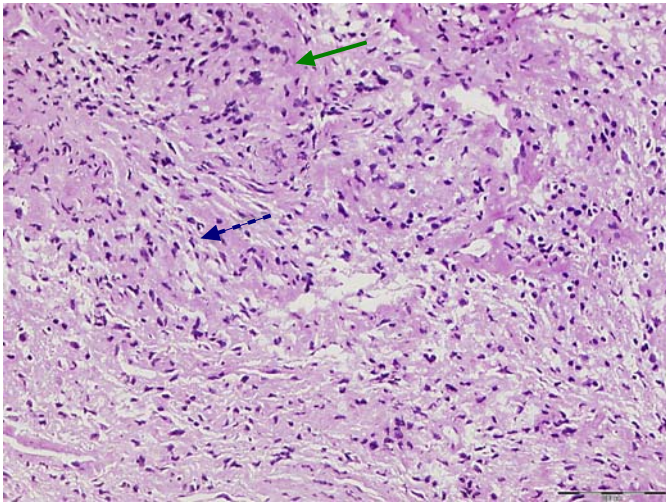
of the left side after opening of the round window which was removed in order to insert the CI into the cochlea. This tissue was sent for histopathological and immunohistochemical analysis. Both CIs had an extremely fast and good effect on hearing and overall the patient was extremely well adapted. He even managed to go snowboarding with bilateral complete vestibular loss.

#### Histopathologic and Immunopathologic Results

Immunohistochemical assays were performed according to standardized staining procedures using machines from Ventana and Medite and the following antibodies: CD3 (cloneSP7), CD163 (163C01/10D6), NF- $\kappa$ B p65 (Rel A) purchased from NeoMarkers/Lab Vision Corp. and CD68 (PG-M1), CD8 (C8/114B), CD20 (L26), CD138 (MI 15), polyclonal anti-CD117 purchased from DAKO as well as CD4 (1F6) were purchased from Novocastra Lab. and polyclonal anti-HO-1 from StressGen Biotech. All antibodies were used according to the manufacturer's recommendations [Dabbs, 2006].

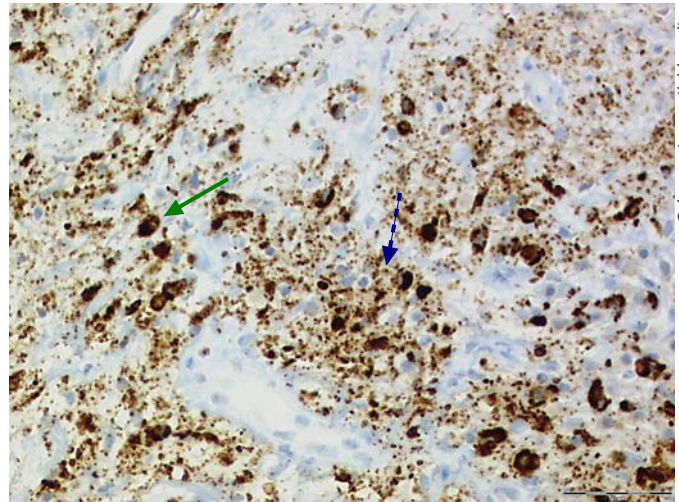
Conventional histology of inner ear tissue, stained with hematoxylin and eosin, showed mild chronic inflammation with the formation of granulomas (fig. 2). The majority of the cellular contents was identified as macrophages by immunohistochemical CD68 and CD163 reactivity (fig. 3).

Some CD3-positive T lymphocytes were also detected. Further staining revealed some CD8-positive suppressor and cytotoxic T cells and negativity for helper/inducer T lymphocytes by CD4 staining (fig. 4). Furthermore, very few CD20-positive mature B lymphocytes were detected, as well as a few CD138-positive plasma cells and very few CD117-positive mast cells. There was strong heme-oxygenase-1 (HO-1) expression (fig. 5), which explains the inflammatory reaction, and strong positivity of the anti-apoptotic nuclear transcription factor- $\kappa$ B (NF- $\kappa$ B) (fig. 6), which mediates at least partly the HO-1 increase.



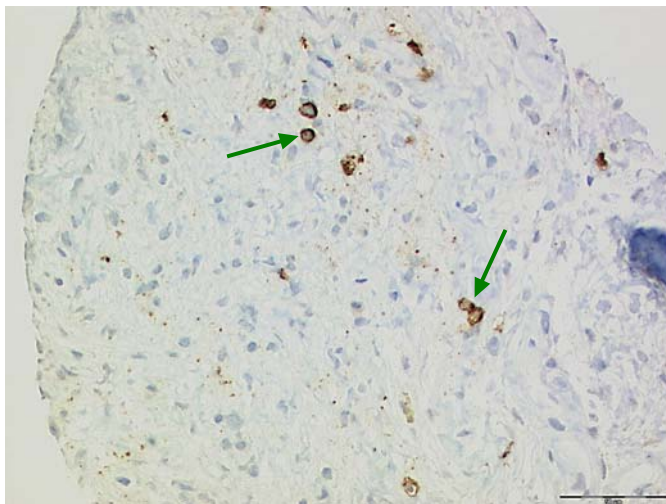
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**Fig. 2.** Mild chronic inflammation with formation of poorly defined granulomas (arrow) and spindle cell macrophages (dashed arrow). Magnification  $\times 100$ .



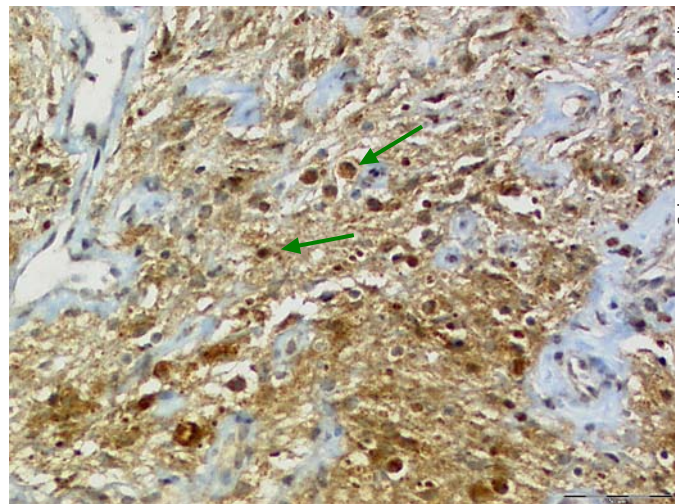
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**Fig. 3.** CD68-positive macrophages are abundant (arrow) and are arranged in poorly formed granulomas (dashed arrow). Magnification  $\times 200$ .



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**Fig. 4.** Some T lymphocytes, expressing CD8 (arrows). Magnification  $\times 200$ .



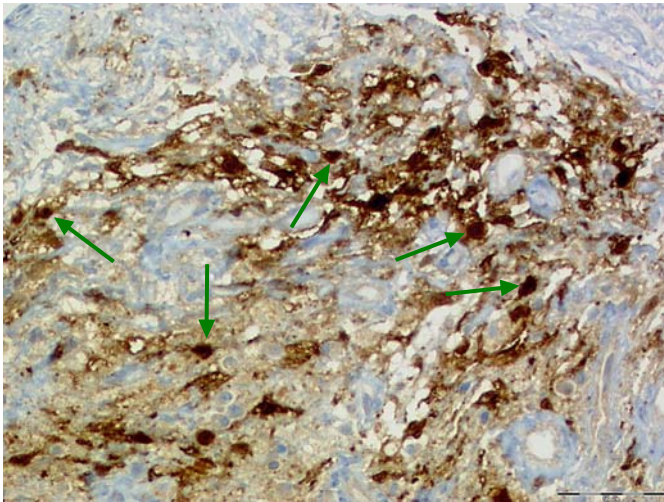
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**Fig. 5.** Strong HO-1 expression in activated macrophages (arrows). Magnification  $\times 200$ .

## Discussion

AIED is a rare cause of SNHL first described in 1979 [McCabe, 1979]. It is important to recognize this disease entity, because early diagnosis and proper management may prevent complete hearing loss. Unfortunately, there is no generally accepted serologic test available for the diagnosis of systemic autoimmune diseases [Dayal et al., 2008].

The pathogenesis of systemic autoimmune diseases remains unclear but antibodies directed against the inner ear and/or cellular effectors have been proposed [Buniel et al., 2009; Harris and Sharp, 1990; Staecker and Lefebvre, 2002; Veldman, 1998]. Among the target antigens associated with progressive SNHL, type II collagens, type IX collagens, 30-kD proteins of inner ear membranes, laminin, 68-kD proteins of the inner ear, PO protein, Raf I protein and  $\beta$ -tubulin have been described [Yoo et al., 2002].



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**Fig. 6.** Strong activation of the antiapoptotic NF-κB (arrows). Magnification  $\times 200$ .

Autoimmune reactivity to the inner ear has been observed as a clinical feature in various systemic immune-mediated disorders, such as Cogan's syndrome, Behçet's disease, Wegener's granulomatosis, systemic sclerosis, systemic lupus erythematosus, giant cell arteritis, panarteritis nodosa and unclassified systemic vasculitis [Stone and Francis, 2000]. Not surprising, it has also been linked to inflammatory bowel disease [Harris and Sharp, 1990; Karmody et al., 2009; Staecker and Lefebvre, 2002]. In an animal model [Harris, 1987] and a histopathological study of the temporal bones in 1 patient with ulcerative colitis, lymphocytic infiltration of the inner ear was found [Hoistad et al., 1998], which is different from our findings but also suggests an autoimmune process. Even an immunohistopathological study does not necessarily imply that the hearing loss is a manifestation of AIED.

As a distinct clinical entity without other immune-mediated disorders, it was termed AIED, but nowadays this term is also used if a typical inner ear disease is coupled with other autoimmune diseases. Being associated with so many different systemic disorders, it is not surprising that the clinical course is extremely variable. This may also reflect different activation stages of differing underlying autoimmune disorders.

In contrast, if AIED is not associated with another autoimmune disorder, it is usually characterized by rapidly developing (weeks or months) and progressive hearing loss [Berrettini et al., 1998].

Typically AIED is first treated with high-dose corticosteroids [Buniel et al., 2009; Dayal et al., 2008; Harris et al., 2003]. If this treatment is insufficient, other drugs like methotrexate may be administered, although in some patients the disease still progresses [Salley et al., 2001]. A newer promising treatment option is the administration of a tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) blocker like infliximab [Staecker and Lefebvre, 2002; Van Wijk et al., 2006]. Since the administration of different medications had no effect in our patient, CIs were applied. We were able to examine some tissue from the patient's inner ear which was removed when the cochlear electrodes were implanted. The tissue studied was in direct contact with the round window membrane and behind it. Histology revealed tissue with poorly formed granulomas and abundant activated macrophages positive for CD68 and CD163 and strongly expressing HO-1. Besides that, there was an infiltrate of mononuclear cells with a strong activation of NF- $\kappa$ B. As our patient suffered from Crohn's disease, it is possible that the granulomas we found in his inner ear were associated with this autoimmune disorder, since they are one of the histological hallmarks of Crohn's disease. On the other hand, sarcoid-like granulomatous reactions are rare but not exceptional in patients treated with TNF blockers (approximately 1/2800) and do not seem to be related to gender, rheumatic disease or type of anti-TNF drug used. As described, they resolve after discontinuation [Daien et al., 2009]. We could not exclude an effect of the TNF-blocking agents in this study.

There is evidence that HO-1 is also involved in this complex autoimmune process in inflammatory bowel disease and provides endogenous antioxidant and anti-inflammatory moieties that can modulate colonic inflammation [Horvath et al., 2008; Paul et al., 2005].

The effector immune cells produce high levels of pro-inflammatory cytokines in inflammatory bowel disease and the NF- $\kappa$ B pathway was identified as one of the key factors in inflammatory bowel disease [Atreya et al., 2008; Ellis et al., 1998].

Crohn's disease is considered a systemic immunopathy that has many well-documented extraintestinal manifestations like joints, eyes or other regions of the head like the larynx, oral cavity and the nose [Aloi and Cucchiara, 2009; Bradley et al., 2004; Lakatos et al., 2003].

The findings described here resemble the histopathological characteristics of Crohn's disease. Therefore, we suggest that our patient did not have classic AIED but might have suffered from an extraintestinal manifestation of Crohn's disease. As in Crohn's disease, not all patients can be successfully treated with standard immuno-

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suppression, and some patients with AIED may require the new TNF- $\alpha$  blockers for beneficial treatment [Rutgeerts et al., 2009; Staecker and Lefebvre, 2002; Van Wijk et al., 2006]. As some patients like ours may still not respond to therapy, there is a need for new treatment options and better characterization of the underlying autoimmune process.

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