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Paraneoplastic Syndrome: A Masquerade of Autoimmune Inner Ear Disease

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Rare and diagnostically challenging, paraneoplastic syndromes can appear months to years before detection of their underlying neoplasms and are associated with rapidly progressive neurologic deficits, including cochleovestibulopathy and death. Less than 20 cases of paraneoplastic cochleovestibulopathy have been reported in the online database PubMed. We present three recent cases: one patient with a history of B-cell follicular lymphoma who developed dermatomyositis and hearing loss before detection of lymphoma recurrence in his anterior chest wall, a second patient with sudden asymmetric hearing loss, found to have a 12-cm renal mass before death, and a third with fluctuating bilateral hearing loss who was ultimately found to have a thymoma. Although characterized as type VI (non-immune rapidly progressive sensorineural hearing loss) within the Harris autoimmune inner ear disease classification system, the mechanism of paraneoplastic cochleovestibulopathy is not well understood. Although specific anti-neuronal antibodies such as anti-Hu may be associated with other paraneoplastic neurologic disorders, these antibodies have limited diagnostic utility with paraneoplastic cochleovestibulopathy. Steroids have limited efficacy with regard to hearing recovery, whereas intravenous immunoglobulin has been shown to be of benefit. These recent cases demonstrate how auditory and vestibular deficits may be indicative of a rare but potentially life-threatening occult neoplasm where timely diagnosis is critical. We believe that understanding paraneoplastic cochleovestibulopathy is of interest across a broad range of clinical practices. **Key Words:** Autoimmune inner ear disease—Paraneoplastic cochleovestibulopathy—Paraneoplastic syndrome.
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Paraneoplastic syndromes are a diverse group of disorders that occur in cancer patients and are caused by mechanisms other than metastases, metabolic abnormalities, nutritional deficits, infections, coagulopathy, or side effects of cancer treatment (1). Commonly recognized paraneoplastic syndromes include myasthenia gravis, Lambert-Eaton myasthenic syndrome (LEMS), and dermatomyositis/polymyositis, whereas paraneoplastic neuronal disorders affecting the central nervous system (e.g., encephalomyelitis, opsoclonus-myoclonus ataxia, stiff-man syndrome) or the peripheral nervous system (e.g., Guillain-Barre syndrome, autonomic neuropathy) are rarer (1). Paraneoplastic cochleovestibulopathy is the term we have coined to indicate a rare manifestation of paraneoplastic neuronal disorders involving rapidly progressive atypical hearing loss or vestibular dysfunction and either diagnosis of an occult malignancy or detection of a known paraneoplastic antibody. Until the occult malignancy or paraneoplastic antibody is confirmed, the diagnosis of paraneoplastic cochleovestibulopathy is often confused with an autoimmune inner ear disease. Less than 20 cases of paraneoplastic cochleovestibulopathy have been reported in the PubMed database. It is unclear if the number of case reports accurately depicts the disease incidence given the difficulty in diagnosis and patients' often rapid decline. In this context, three recent cases from the authors' practices are presented with the goal of further describing this rare pathology.

Most previously reported cases of paraneoplastic cochleovestibulopathy involve sudden onset bilateral sensorineuronal hearing loss refractory to high-dose oral, IV, or intratympanic steroids, with worsening neurologic symptoms such as ataxia (2,3), vertigo (4), and

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opsoclonus-myoclonic seizures (5), often leading to death. Paraneoplastic neuronal disorders are most commonly associated with small-cell lung cancer (6), but have also been associated with other types of lung and breast cancers, lymphoma, thymoma, and other tumors (6). In many cases, the diagnosis was made after rapid neurologic decline and often at autopsy. The median survival time from onset of paraneoplastic neurologic symptoms is unclear as studies of larger patient groups (rather than single case reports) vary from 7 months (2) to 43 months (6). There are no large-scale studies demonstrating survival time of patients with paraneoplastic cochleovestibulopathy specifically and individual case reports also are variable. Diagnosis of paraneoplastic cochleovestibulopathy has frequently depended upon the paraneoplastic panel or anti-neuronal antibodies associated with paraneoplastic syndromes such as anti-Hu (2,7), anti-Yo (8), anti-Ri, anti-Tr, anti-CV2/CRMP5 (Collapsin response mediator protein 5), anti-Ma (9), and anti-amphiphysin (1,10), although many of these are incompletely characterized and have been found to occur with and without an associated cancer (1,3,10–12), limiting their clinically utility.

METHODS

A literature search of case reports of fitting our classification of paraneoplastic cochleovestibulopathy (sudden onset bilateral sensorineural hearing loss refractory to typical steroid or other treatments accompanied by other neurologic symptoms including vestibular dysfunction and either diagnosis of an occult malignancy or a positive paraneoplastic antibody) was undertaken using the PubMed database and the keywords ''paraneoplastic,'' ''hearing loss,'' and ''cochleovestibulopathy.'' One case report was excluded because the onset of hearing loss occurred after chemotherapy treatment for small cell lung cancer as well as clinical improvement with IV acyclovir, suggesting herpes simplex virus (HSV) encephalitis as the etiology (13). Another case report of anti-Hu antibody positive patients with small cell lung cancer and a variety suspected paraneoplastic neuronal disorders mentions patients with cranial nerve (CN) VIII neuropathy was excluded because of paucity of details (no audiogram, time course of hearing loss, etc.) (14). Other case reports were excluded as they lacked sufficient detail (15) or were not translated into English.

The records of the three patients arose from the clinical practices of three of the four authors (M.W.K., J.P.H., A.J.M.). Each patient underwent a thorough otolaryngologic history and examination, including pure-tone testing at standard audiometric frequencies (250–8,000 Hz in octave steps). All patients had serum collected and tested for paraneoplastic antibodies. Patients 1 and 3 underwent additional testing, including electrocorticography (ECoG), vestibular-evoked myogenic potential (VEMP), and electronystagmography. Screening for occult malignancy that included MRI and PET/CT imaging was completed for Patients 1 and 3, but only MRI and CT imaging for Patient 2.

RESULTS

Case Reports

A literature review of cases of paraneoplastic cochleovestibulopathy is presented in Table 1. Many but not all patients had their serum and/or cerebrospinal fluid (CSF) tested for paraneoplastic antibodies. The most common paraneoplastic antibody was anti-Hu, although several other patients tested positive for anti-AChR Ab, anti-VGKC Ab, and anti-GAD65 Ab. With one exception, all patients had confirmed neoplasms including small cell lung carcinoma (SCLC), ovarian adenocarcinoma, neuroblastoma, non-Hodgkin's lymphoma, thymoma, and clear cell carcinoma. The most common neoplasm was SCLC and thymoma. The one patient without a detected neoplasm had myenteric ganglionitis in addition to bilateral sensorineural hearing loss (SNHL) and confirmed serum and CSF anti-Hu antibodies (3). It is important to note that for some of the older case reports, discovery of the occult neoplasm was not made until just before death or upon autopsy.

Along with these published cases of paraneoplastic cochleovestibulopathy, we report three new cases along with audiograms.

Case 1

A 41-year-old man with a history of non-Hodgkin's lymphoma in remission (underwent chemotherapy in 2008 [R-CHOP and Rituxan] and an autologous stem cell transplant in 2010) presented in 2013 with 4 months of intermittent bilateral SNHL. An audiogram (Fig. 1A) revealed moderate and moderate-to-severe SNHL for the left and right ears, respectively. He had also complained of proximal upper and lower extremity weakness and a facial rash and underwent electromyography and a muscle biopsy that revealed dermatomyositis and had been started on prednisone. The hearing loss was bilateral and intermittent; according to the patient, it seemed to worsen after taking his prednisone. Although suspected of having paraneoplastic cochleovestibulopathy, the serum paraneoplastic panel was negative. Additionally, PET/CT imaging demonstrated recurrence of follicular B-cell lymphoma in the left anterior chest wall. The patient was started on monthly intravenous immunoglobulin (IVIG) therapy with a 10 to 20 dB improvement in hearing across all frequencies within 6 months (Fig. 1B). The patient currently uses hearing aids; the chest mass was later resected.

Case 2

This 47-year-old woman with no significant medical history presented with symptoms of initially left SNHL that rapidly progressed to bilaterally profound SNHL within 3 weeks (Fig. 1, C and D). Her screening MRI internal auditory canal was negative, and a course of high-dose prednisone for the hearing loss was ineffective. Her serology was positive for syphilis (fluorescent treponemal antibody absorption but negative rapid plasma reagin, Venereal Disease Research Laboratory [VDRL]) but her CSF VDRL was negative and CSF culture was negative. The rapid timeline of her hearing loss, as well as additional neurologic symptoms including diplopia, ataxia, and tinnitus, were not consistent with the presumptive diagnosis of neurosyphilis. She was treated with IV penicillin as well as intratympanic injections of dexamethasone without improvement. The diagnostic differential included

TABLE 1. *Summary of cases of paraneoplastic cochleovestibulopathy*

Study or MD reporting case	Age	Sex	Other clinical pathology in addition to SNHL	Paraneoplastic panel	Onset of SNHL before neoplasm detection	Underlying malignancy	Outcome
Dalmau et al. 1992	60	F	Ataxia (midline cerebellar syndrome)	Positive anti-Hu	4 mo	SCLC (mediastinum)	SCLC detected 1 wk before death
Gulya et al. 1993 (case dates to 1969)	56	F	Vertigo upper extremity atrophy dysesthesia	Unknown	9.5 mo	SCLC (1.5 cm right upper lobe)	Passed away from bronchopneumonia and neurologic deterioration
Gulya et al. 1993 (case dates to 1988)	74	F	Vertigo Altered mental status Dysphagia	Unknown	2 mo	Serous adenocarcinoma (L ovary)	Despite ovarian tumor resection and pelvic exenteration, passed away 4 mo later
Fisher et al. 1994	1	F	Opsoclonus-myoclonus developmental regression seizures	Positive anti-Hu	3 mo after tumor resection	Neuroblastoma	Neuroblastoma resected, OM and seizures improved, decreased anti-Hu titers with IVIG but has remained deaf
Rinne et al. 1998	—	—	Vertigo oscillopsia lymphadenopathy	Unknown	Unknown	Non-Hodgkin's lymphoma	Not known, suggested paraneoplastic etiology
Basilisco et al. 2005	35	M	Intestinal pseudo-obstruction Myenteric ganglionitis Ataxia	Positive anti-Hu	Unknown	None detected	Improved over 5 yr with IV steroids but permanent hearing loss and ataxia
Vernino et al. 2004	—	—	Myasthenia gravis	Positive anti-AChR, anti-VGKC	2 wk	Thymoma	Unknown
Vernino et al. 2004	—	—	Vertigo	Positive anti-GAD65	Unknown	Thymoma	Unknown
Chong et al. 2005	58	F	Vertigo proximal weakness altered mental status	Positive anti-Hu	1.5 mo	Anaplastic SCLC	Palliative care, passed away
Hirst et al. 2007	43	M	Vertigo Ataxia Seizures Pathologic hip fracture Altered mental status	Unknown	2 mo	Clear cell carcinoma	Became profoundly deaf 1 yr after partial nephrectomy with neurologic status deterioration, passed away
Evoli et al. 2007	—	—	Myasthenia gravis	Unknown	Unknown	Thymoma	Unknown
Matsuoka (case dates to 2013)—Case 1	42	M	Polyarthritis Dermatomyositis	Negative	1.5 yr	Non-Hodgkin's lymphoma	Survived, uses hearing aids
Keefe (case dates to 2008)—Case 2	42	F	Dizziness	Negative	5 mo	Renal neoplasm	Despite nephrectomy, developed profound deafness, blindness, ataxia and passed away
Harris (case dates to 2011)—Case 3	40	F	Vertigo Ataxia	Negative	1–2 yr	Thymoma	Survived, cochlear implants

SNHL indicates sensorineural hearing loss; SCLC, small cell lung carcinoma.

autoimmune inner ear disease (however, antibodies to 68 kDa were negative, anti-nuclear antibody negative) versus Susac's disease (angiography negative) versus Cogan's disease (no evidence of uveitis). Workup for other infectious etiologies, including West Nile, cytomegalovirus, HSV, human immunodeficiency virus, or other autoimmune pathologies including lupus and multiple sclerosis, were all negative.

She developed a urinary tract infection and a renal ultrasound demonstrated a 12-cm renal cancer, 5 months after her initial presentation of hearing loss. Her CSF was tested for paraneoplastic antibodies and found to be negative, but was treated with IVIG for a presumed paraneoplastic encephalitis without response. CSF flow cytometry was negative for any clonality lymphoproliferative disorder, and a single gamma band was deemed insufficient to diagnose multiple sclerosis. A repeat MRI for her declining mental status only demonstrated nonspecific white matter changes without enhancement and a CT Brain was likewise negative. Despite further treatment with nephrectomy, the patient developed profound deafness, blindness, and ataxia, and she ultimately passed away from aspiration pneumonia.

Case 3

This 40-year-old woman with a history of postural orthostatic tachycardia syndrome presented with 3 years of dizziness and tinnitus and a 1-year history of worsening bilateral hearing loss, otalgia, and aural fullness. Audiogram revealed a 50 to 60 dB bilateral SNHL (Fig. 1E). She was initially suspected of having Ménierè's disease and was treated with hydrochlorothiazide without improvement. Pressure equalization tubes were placed for the aural fullness with limited relief. The patient also had fevers, weight loss, rashes, and a positive antibody test for heat shock protein 70 (HSP70), suggesting an autoimmune

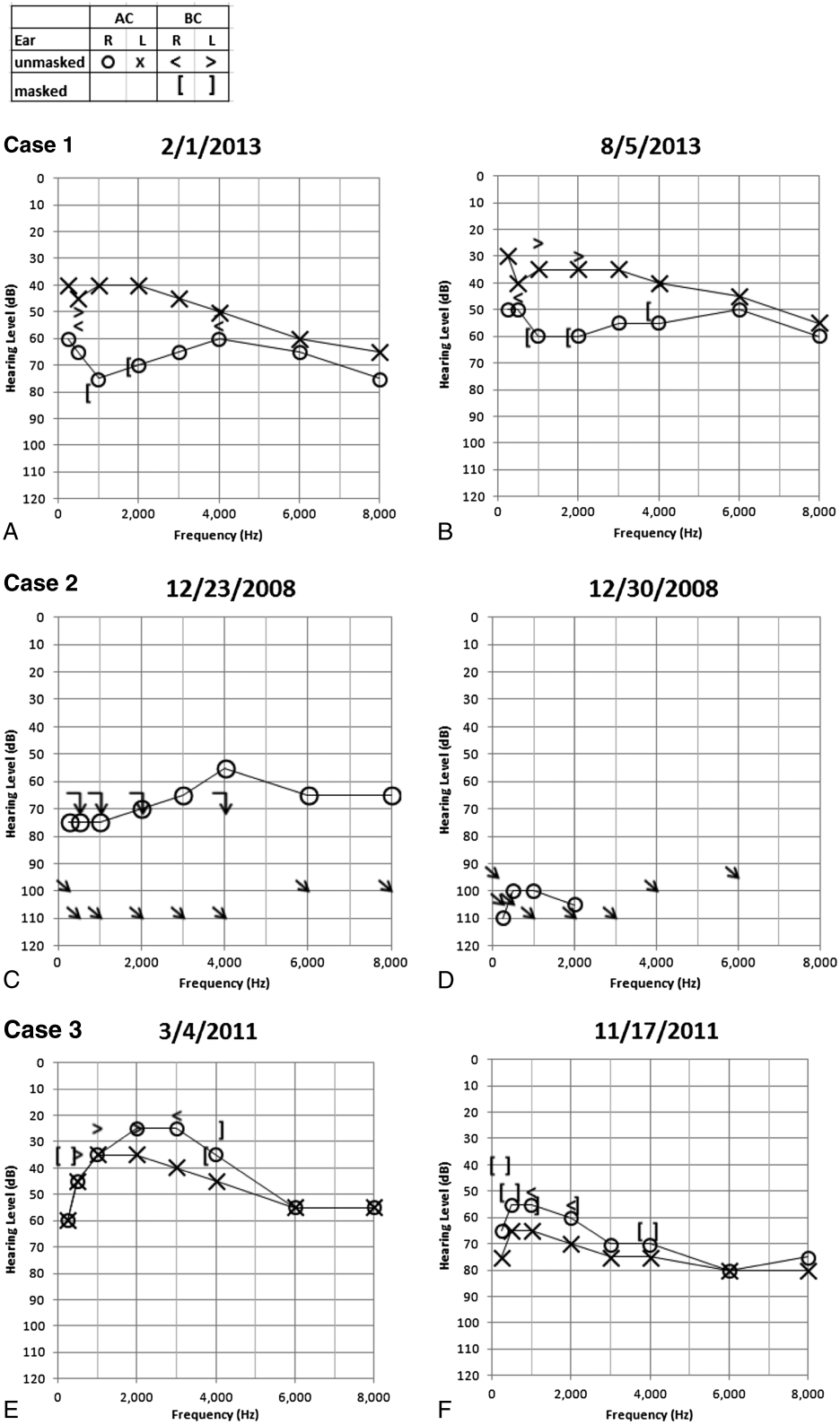

FIG. 1. Audiograms of (*A*) Case 1 on initial presentation and (*B*) after treatment with IVIG, (*C–D*) Case 2 upon presentation and 1 week later, and (*E–F*) Case 3 on presentation and after steroid treatment.

etiology. However, there was no improvement from multiple trials of high-dose oral prednisone and IT-administered dexamethasone (Fig. 1F). She was treated with a high-dose prednisone taper (60 mg daily × 2 wk, 40 mg daily × 2 wk) without hearing improvement. All serological tests, including the C-reactive protein test, a Lyme titer, a rheumatoid factor test, and a fluorescent treponemal antibody absorption test, were negative. A serum paraneoplastic panel was ordered for anti-neoplastic ANNA-1 (anti-Hu) and ANNA-2 (anti-Ri) antibodies; results were negative. Videonystagmography (VNG) findings were normal aside from unilateral borderline weakness (23%). No retrocochlear lesions were detected on MRI. The patient failed all of the treatments, including biological modifiers. The patient was found to have a thymoma which was surgically resected; however, her hearing loss persisted and she has since become a candidate for a cochlear implant.

Summary of the Three Cases

All three patients had rapid onset, bilateral SNHL on audiometric testing and had negative paraneoplastic antibody panels. Case 2 was negative for the HSP70 antibody, whereas Case 3 tested positive. All patients were treated with prednisone with limited benefit. All patients had onset of hearing loss before detection of neoplasm, although in Patient 1 this was detection of neoplastic recurrence. Once paraneoplastic cochleovestibulopathy was suspected, most patients underwent screening for malignancy including MRI, CT, and PET imaging. The neoplasms detected varied from recurrence of non-Hodgkin's lymphoma in the anterior chest wall, a thymoma, and renal cancer. Case 1 was treated with IVIG and had a 10 to 20 dB improvement in hearing across all frequencies. While Case 1 and 3 survived, the patient in Case 2 ultimately passed away despite resection of the renal neoplasm.

DISCUSSION

Definitive diagnosis of paraneoplastic cochleovestibulopathy is difficult given the low sensitivity of the paraneoplastic panel and occult malignancy, but typically involves a rapidly progressive, atypical unilateral or bilateral hearing loss unresponsive to typical therapies and confirmed by either a known paraneoplastic antibody or evidence of an occult neoplasm. Perhaps the most convincing diagnosis of paraneoplastic cochleovestibulopathy was reported by Gulya (4) in which a 56-year-old woman with a history of sudden, asymmetric, severe SNHL, neurologic decline, and ultimate death 8 months later was found on autopsy to have a 1.5-cm SCLC and whose temporal bone revealed total loss of the cochlear and vestibular nerves; no paraneoplastic panel was reported. Unfortunately, temporal bone pathology is rarely reported even when autopsies are performed. An international panel of neurologists developed criteria to determine if paraneoplastic neuronal disease was ''definite'' versus ''possible'' and involved the classical paraneoplastic syndromes (encephalomyelitis, limbic encephalitis, subacute sensory neuropathy, chronic gastrointestinal pseudo-obstruction, LEMS, or dermatomyositis) and either discovery of cancer within 5 years of diagnosis or definitive antibodies (10). Within this schema, paraneoplastic cochleovestibulopathy is a non-classical neurological syndrome, and the patients in this study had no paraneoplastic antibodies, but did have cancer diagnosed within 2 years of their symptoms and thus would be classified as possible paraneoplastic neuronal disease (10). Dermatomyositis has been reported as a paraneoplastic disorder associated with several types of malignancies including non-Hodgkin's lymphoma as seen in Case 1 (16,17).

Pertinent medical history, including past cancers (such as the history of lymphoma with Case 1) and autoimmune disease, are important to investigate. If paraneoplastic cochleovestibulopathy is suspected, initial workup should include audiometric testing including VEMP, ECoG, and VNG and the patient should be worked up for an occult tumor including possible whole-body PET CT and sending serum or CSF for paraneoplastic antibody panels as neurologic symptoms may precede diagnosis of the malignancy. Although a small tumor may be missed on imaging, other imaging findings such as hyperintensity of the acoustic nerves on MRI may be suggestive of a paraneoplastic process (15). It is also critical to obtain an MRI of the internal auditory canal and brain to rule out any cerebellar involvement.

Other causes of autoimmune inner ear disease should also be investigated and ruled out. Current treatment for autoimmune inner ear disease involves an initial course of high-dose prednisone (60 mg/d) for 4 weeks with a taper to a maintenance dose based on hearing (1,18), although paraneoplastic cochleovestibulopathy does not typically improve with steroids (11). Other immunosuppressants such as Humira and Rituxan have shown some benefit in autoimmune inner ear disease (AIED); however, whether they may demonstrate efficacy in paraneoplastic SNHL remains to be seen (18,19). Although other paraneoplastic syndromes such as myasthenia gravis or Lambert-Eaton are responsive to plasmapheresis and immunomodulation, it is unclear whether paraneoplastic hearing loss responds (1). If a patient is suspected of having paraneoplastic neuronal disorders and is positive for anti-neuronal antibodies but has negative imaging for neoplasm, it is recommended that they undergo screening every 6 months (1) for at least 2 to 3 years (17).

The ultimate therapy for paraneoplastic cochleovestibulopathy would be treatment of the underlying tumor before neurologic deterioration and death occurs; however, given the rapidly progressive nature of this disease along with its rarity, this has proven challenging. In one retrospective study of patients with paraneoplastic disorders, patients who received treatment for their malignancy (radiation, chemotherapy and/or surgery, with or without immunomodulation) were 1.5 times more likely to have stable or improved neurologic disease (6). Immunomodulation has not been shown to significantly treat or improve patients with paraneoplastic neuronal disease (6,17,20,21); however, many individual cases of improvement with IVIG, as Case 1

in this report, have been reported (6). In one study of patients with paraneoplastic cerebellar degeneration, patients treated with IVIG within 1 month of symptoms had a better response than those treated after 3 months, who typically had a poor outcome (8). It has been suggested that malignancies causing paraneoplastic neuronal disorders remain occult because of effective antitumor immunity (22), which raises the issue if immunosuppression would promote tumor growth. There is no evidence that immunosuppression or IVIG favors tumor growth, although further immunosuppression for a patient undergoing chemotherapy has inherent risks with regards to infection susceptibility (1), and IVIG has also been linked to rare cases of anaphylaxis (19). There is no data regarding treatment efficacy for patients with paraneoplastic cochleovestibulopathy.

Paraneoplastic neurologic disorders have been reported to precede the diagnosis of the neoplasm in 80% of cases (6) and the median time of survival from the first neurologic symptom and death was reported as 43 months (6). Given the risk of rapid neurologic decline, it is critical to initiate a thorough screening for the underlying malignancy once paraneoplastic process is suspected (19). The three patients described in this study had hearing loss and other neurologic symptoms including vertigo and ataxia that preceded tumor detection from 5 months to 1 to 2 years. For many of the case reports of paraneoplastic cochleovestibulopathy within the literature (Table 1), tumor diagnosis was often shortly before death or on autopsy.

Paraneoplastic cochleovestibulopathy has been classified within the Harris AIED classification schema as type VI, given the evidence of inflammatory infiltrates on autopsy (4,23) and oligoclonal bands on CSF (6,17) and reported response to immunomodulation, although steroids are usually ineffective (18). Autoimmune hearing loss is also observed from Wegener's granulomatosis, Cogan's syndrome, rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, or relapsing polychondritis (18,24). Autoimmune inner ear disease has been linked to an antibody against a 68-kDa inner ear antigen, believed to be HSP70 (24); however, the HSP70 antibody test was not found to be sufficiently sensitive to detect AIED in one retrospective study (18). Patient 3 in this study tested positive for the HSP70 antibody; Patients 1 and 2 tested negative.

The reported incidence of paraneoplastic neuronal disease (PND) with confirmed antibodies is variable likely because of varying clinical criteria for ''suspected'' PND and so it is difficult to assess the utility of the paraneoplastic panel. One study of 60,000 suspected cases of PND only had 553 patients with confirmed antibodies, or 0.9% (25), although another retrospective study of 57 suspected cases of PND demonstrated a 77% positive test for paraneoplastic antibodies (6), whereas unpublished data from Dalmau et al. reports a 25% positive paraneoplastic panel in 649 patients with suspected PND (12). In a recent study of 219 patients with clinically diagnosed paraneoplastic cerebellar degeneration, 39 patients (18%) tested negative for classical onconeural antibodies (seronegative) (26). However, if a patient tests positive for a paraneoplastic antibody, the likelihood of a concurrent neoplasm is fairly high as evidenced by one retrospective study of 55 patients with cerebellar degeneration and a paraneoplastic panel positive for anti-Yo antibody in which 52 were found to have malignancies (27). A Cochrane review of treatment for paraneoplastic disease found insufficient data to conclusively determine the prognostic value of the paraneoplastic antibodies (20), and as can be seen from this study, Cases 1 and 3 tested negative for serum paraneoplastic antibodies whereas Case 2 tested negative for CSF paraneoplastic antibodies. A negative paraneoplastic panel should not be used to rule out a paraneoplastic process (28).

An additional limitation of the paraneoplastic panel as a means of diagnosing a paraneoplastic neuronal disorder is that the library of known paraneoplastic antibodies is evolving. A new autoantibody that targets glutamate receptors was reported in two patients with cerebellar ataxia that developed while they were in remission from Hodgkin's disease (29). It is important to note that auditory and vestibular neurons are in fact glutamatergic neurons. Another anti-glutamate receptor antibody was discovered in patients with Rasmussen's encephalitis, a severe form of intractable childhood epilepsy, but no routine diagnostic assay is available for this antibody (30). Anti-DNA antibodies that cross-react with the *N*-methyl-D-aspartate receptor (member of the glutamate receptor family) have been reported in patients with systemic lupus erythematosus and various neuropsychiatric symptoms (30).

There are many reported cases of patients with suspected paraneoplastic neuronal disorders who test negative for paraneoplastic antibodies. In one study of 21 patients with cerebellar degeneration and Hodgkin's disease, only six patients had serum antibodies reactive with Purkinje cells but were distinct from anti-Yo and anti-Hu, but no Purkinje cell antigen was discovered and there was no difference clinically between seropositive and seronegative patients (31). In this study, it was theorized that paraneoplastic antibodies were not detected possibly because of low antibody titers, fragile or labile antibodies destroyed by routine laboratory processing, strong binding affinity to tissue preventing solubility in serum or CSF, or possibly that this paraneoplastic process is not humorally mediated (31). Another possibility is that although some paraneoplastic antibodies targeting intracellular antigens are actually reacting with denatured polypeptides presented on the cell surface via major histocompatibility complexes, others are targeting external structures like ion channels that can only be measured utilizing intact native proteins with radioimmunoprecipitation assays with detergent-extracted ion channels (30). Another possibility to explain why some patients test negative for paraneoplastic antibodies is that the titers may peak and change over time, as seen in limbic encephalitis with anti(30)-VGKC antibodies (30) or one of the cases included in Table 1 with positive anti-Hu antibody (3).

The mechanism of paraneoplastic cochleovestibulopathy remains unclear. Tumor-produced anti-neuronal antibodies may have a direct pathogenic effect, such as the antibodies that target voltage-gated calcium channel in LEMS (1),

whereas others merely induce an immune attack on normal tissue such as anti-ds-DNA in rheumatologic disease or anti-neuronal antibodies (32). Many of the antigens targeted by paraneoplastic antibodies are intracellular (33), such as Hu antigens that are 35- to 40-kDa proteins expressed in the nucleus and cytoplasm of all central nervous system and peripheral nervous system neurons as well as most small cell lung cancers and 50 to 78% of neuroblastomas (7). Additionally, different paraneoplastic antibodies may coexist in the same patient, demonstrating multiple autoantigens and the subsequent multifocal nature of paraneoplastic neurologic disorders (25). Thus, paraneoplastic anti-neuronal antibodies may be mere markers of the presence of a tumor and a systemic T-cell–mediated attack on neuronal tissue than directly pathogenic (23,34,35). In one study, Hu antigen injected intravenously into live animals resulted in elevated titers of anti-Hu antibody but without evidence of further clinical pathology (7,23,36), whereas transfer of T cells targeting onconeural antigens can cause encephalomyelitis in genetically engineered rats expressing that same antigen (35).

It may be that paraneoplastic antibodies are only a small part of the disease process of paraneoplastic cochleovestibulopathy and that the actual mechanism is much more complex. The burgeoning field of epigenetics, which examines methods of gene regulation such as DNA methylation, histone modification, nucleosome positioning, and microRNAs, have demonstrated that such mechanisms may explain differences in concordance rates of autoimmune disease between monozygotic twins who otherwise have identical DNA sequences (37). New genome-wide association studies have investigated gene regulation of autoimmune diseases such as multiple sclerosis and have found differences in expression of transcription factors EOMES and TBX21 that control differentiation of T, B, myeloid, and NK cells among patients with MS compared to healthy controls (38) as well as for many other autoimmune diseases (39).

CONCLUSIONS

Given the rarity of reports of paraneoplastic cochleovestibulopathy and diagnostic difficulty, limited conclusions can be drawn from these three recent cases. The paraneoplastic panel and other antibody tests have shown little utility in diagnosis of paraneoplastic cochleovestibulopathy, and may in fact incorrectly be used to rule out a paraneoplastic disorder. Steroids are not typically helpful, although other forms of immunomodulation such as IVIG have been shown to improve some patients' hearing loss. If paraneoplastic cochleovestibulopathy is suspected, thorough laboratory and imaging investigation should take place as paraneoplastic cochleovestibulopathy may be the sole presenting symptom of an otherwise occult malignancy that may lead to rapid neurologic decline and death.

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