Systemic Wegener’s Granulomatosis with Severe Oculo-Otological Manifestations

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Abstract
A case of Granulomatosis with Polyangiitis (Wegener’s) is described in which the common presenting symptoms were hoarseness, deafness and ocular manifestations including marked redness and congestion of both eyes. The case findings and other systemic involvements are reviewed briefly along with histological and immunological discussions.

Introduction
Granulomatosis with polyangiitis (Wegener’s) abbreviated as GPA is an alternative new term for Wegener’s granulomatosis. The word granulomatosis here signifies the history of the disease name as well as a main feature of the pathology. The physicians clinical and research work often are focused on vasculitis. The word polyangiitis reflects frequent vasculitic involvement of multiple type of vessels. The Boards of American College of Rheumatology, the American Society of Nephrology and the European League Against Rheumatism proposed inclusion of the parenthetical term (Wegener’s) for several years to help smooth adaptation of the new name. The disease is primarily a systemic vasculitis of unknown etiology that typically affects the upper and lower respiratory tracts and kidneys, however, any organ may be involved. The diagnosis is supported histologically by presence of granulomatous inflammation of arterioles with parenchymal necrosis. The pulmonary nodules with necrotizing inflammation of upper respiratory tract and glomerular nephritis are common systemic features seen in classical and complete forms of Wegener’s granulomatosis. Eye involvement is frequent and may range from mild conjunctivitis to dacroyocytisitits, scleritis, episcleritis, granulomatosis, uveitis, ciliary vessel vasculitis and retro-orbital mass lesion. Retinal vasculitis is seen rarely. Otolological involvement may occasionally be the first and only sign of the disease. The different modes of involvement are otitis media with effusion, acute otitis media and sensory neural hearing loss, otalgia, otorrhea with middle ear involvement in various case reports. Our case illustrates the aftermath of the unusual presentations of aural, ocular and subglottic inflammatory pathology.

Case History
MJ is 50 yrs male patient whose history dates back to 2 years when he presented with purulent discharge from both ears and subsequently developed bilateral hearing loss. In January 2009 he was diagnosed to have chronic bilateral suppurative otitis media with tympanic membrane perforation. Audiogram then done revealed mixed hearing loss, right more prominent than left. He was also examined for his recurrent sino-rhinal symptoms. CT examination revealed multiple nasal scabs, nasal septum deviation, pansinusitis with osteomeatal complex blockade. Two months later he developed hoarseness of voice. ENT examination revealed vocal cord edema and laryngeal congestion. A neurophysician was consulted who recommended short course steroid therapy for possible patchy meningitis and lower cranial nerve palsies, however patient did not show any significant improvement on steroid therapy. The nasal and sinus problems persisted despite steroid therapy. A month prior to the current hospitalization, he developed marked redness, congestion and photophobia of both eyes. The case was referred to Mumbai for the repeat neurophysician consult in September 2009, where he was provisionally diagnosed with cerebropontine tumor, however MRI done at that time didn’t reveal any pathology.

Patient presented to our hospital in October 2009 with symptoms of deafness, headache, hoarseness of voice and redness of eyes. Patient denied any history of leutic infections or blood transfusions in past. His past medical history is negative for Diabetes, Hyperlipidemias, CVA, CHD or any other chronic illnesses. Review of systems was significant for weight loss of 7 kg over a period of 5 months.

The clinical examination revealed normal vital parameters. There was no signs of cyanosis, icterus, pallor, clubbing, pedal edema or lymphadenopathy. Patient had marked chemosis, congestion of both eyes - right affected more than the left (Figure 1). Pulmonary and cardiovascular examinations were unremarkable. Patient’s haemogram revealed 5% peripheral eosinophils, TLC 11,800/cumm and haemoglobin – 12.5 gm%. CRP was positive with 1:8 dilution approximately 56 ugms/ml (latex agglutination test), EsR was 12mm at the end of 1st hour, RA Factor was positive, HIV and HBsAg reported negative. Urine examination showed 4-5 RBC/ HPF and traces of albumin with granular and RBC casts. Renal and liver functions were normal. Repeat chest X-ray revealed few nodular shadows bilaterally admeasuring 1-1.5 cm in diameter (Figure 2). Because of disseminated lesions observed in this case, a possibility of disseminated Granulomatosis with polyangiitis (Wegener’s) was strongly considered. ANCA done was reported positive in 1:640 (normal 1:20) by IFA. The laboratory reported test sensitivity and specificity 86.4% and 86.9% respectively. CT sinuses revealed bilateral maxillary, frontal and ethmoidal sinusitis, mucous membrane thickening, osteomeatal complex blockade bilaterally with bulky right lacrimal gland.

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ENT examination revealed saddle nose, multiple nasal scabs, granulomatous lesions in right nostril. The mucosal biopsy was obtained and the histopathological findings were consistent with granulomatous disorder (Figure 3). Bronchoscopic examination revealed edematous vocal cords with immobile left vocal cord, ulcerations and granulomatous lesions in the right side major bronchus close to carina along with near 60% subglottic stenosis. Ophthalmology was consulted and their detailed examination revealed RE chronic iridocyclitis, with scleritis and LE broken posterior synechiae (Figure 4A). Fundoscopic examination revealed normal RE but LE showed multiple dot haemorrhages along the infero-temporal veins and around fovea, dilated and tortuous blood vessels around the disc (Figure 4B). Fundus fluorescein angiography done revealed normal RE and LE examination significant for 1. Delayed venous filling by 8 second. 2. Late staining of venules and capillaries s/o vasculitis. 3. Staining of optic nerve head seen in late phase. The patient was placed on oral Prednisolone 1mg/kg body weight and cyclophosphamide 2mg/kg/day body weight observing NIH protocol. The beneficial effects were observed clinically within a short span of time viz. 8weeks post therapy. He was last seen about 6 months back while on this same regimen as described above without any major adverse effects and abnormalities in blood counts.

**Discussion**

The multisystemic clinical involvement in Granulomatosis with polyangitis (Wegener’s) is a result of underlying primary vasculitis involving small arteries and veins. The feature is supported histologically by presence of granulomatous

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**Fig. 1**: Face profile showing ocular involvement with redness, chemosis chiefly right eye with saddle nose.

**Fig. 2**: Nasal mucosal biopsy (H+E) x 40 magnification showing granuloma formation.

**Fig. 3**: Chest radiograph (postero-anterior view) showing 1 to 1.5 cm nodules involving bilateral lung fields.

**Fig. 4A**: Photograph left eye showing broken posterior synechiae, suggestive of old iridocyclitis.

**Fig. 4B**: Showing multiple dot hemorrhages along the infero-temporal veins and around fovea with dilated and tortuous blood vessels around the disc.
inflammation of arterioles with parenchymal necrosis. Upper and lower respiratory tract involvement and glomerulonephritis are common systemic features seen in classical form of Wegener’s disease as in this case. The present case is atypical, as otological and ophthalmic involvement though known, are rare occurrences. The eye involvement may range from mild conjunctivitis to sclero-uveitis and retinal haemorrhages. The change may be potentially threatening for vision loss. Pakarou et al in 2006 showed that ocular involvement occur in upto 60% of the cases and presentations varied in extent and severity. The various ophthalmic manifestations described include conjunctivitis, episcleritis, scleritis, ulcerative keratitis, uveitis, uveo-scleritis, retinitis, retinal vasculitis, exudative retinal detachment, retinal vascular disease, nasolacrimal duct obstruction, optic neuropathy and ocular cranial neuropathies. The orbital inflammation in Wegener’s granulomatosis could either be primary vasculitic process or due to contagious spread from paranasal sinuses. The present case has shown evidence of chronic iridocyclitis, scleritis, retinal haemorrhages with inferior semi-central retinal vein occlusion. The retinal vasculitis is described very rarely. Out of 140 patients of Wegener’s only 18% demonstrated retinal disease with retinal haemorrhages and edema. The retinal vascular occlusion has been reported exceptionally. Retinal vasculitis as an isolated feature is known to exist in varied infective and non infective pathologies. Retinal vasculitis seen in infective Chorio-retinitis like Herpes simplex, Herpes zoster, Cytomegalovirus retinitis, Toxoplasmosis are often associated with other characteristic feature of retinal inflammation which are specific of those infective conditions. The present case has strong clinical, histopathological and immunological base for the diagnosis and hence serological profile for virus infections were not undertaken in the case.

The case described here has a common presenting symptom of aural discomfort and discharge. Otological involvement is reported as occurring in 38% of all cases and may represent the only feature of the disease. This patient under discussion had otitis media, discharge from both ears followed by chronic mastoiditis, perforation of TM and mixed severe sensory neural hearing loss. The ear involvement can take place in number of ways with symptoms of 1) Otitis media with effusion which may occur unilaterally or bilaterally caused by eustachian tube obstruction. 2) Acute otitis media wherein granulomatous destruction may result in dissemination of disease to middle ear, mastoid cavity and temporal bone. Facial nerve palsy also has been reported. In our case MRI Brain findings revealed e/o facial neuritis without any clinical depiction. None of the cases had tympanic membrane perforation in Fenton Sullivan series. 3) Sensory neural hearing loss may be noted in such patients. Deposition of immunocomplexes in cochlea, granulomatous compression of cochlear nerve and cochlear nerve vasculitis may be responsible for the damage. Vertigo with vestibular involvement may be unusual presentation in some as against cochlear features which presents with otological manifestations. A high clinical suspicion is important for the diagnosis of this entity with otological manifestations that often fail to respond to the conventional therapeutic measures.

Antineutrophilic anticytoplasmic antibody (cANCA) is very specific of WG and is being used for diagnosis and monitoring the disease. ANCAs are responsible for inflammation in Wegener’s disease. The typical ANCAs in Wegener’s are those that react with proteinase 3, an enzyme prevalent in neutrophil granulocytes. This type of ANCA is also known as cANCA with the ‘c’ indicating cytoplasmic in contrast to pANCA which is perinuclear. The exact cause of production of ANCAs is unknown. Many autoimmune disorders, drugs and probably genetic predisposition combined with molecular mimicking caused by viruses or bacteria may be responsible for the production of ANCA.

Upper airway involvement is an important and often missed complication of this granulomatous disorder as was noted in the case. The x-ray chest revealed nodular shadows on either side but patient had no pulmonary symptoms. However, he had hoarseness of voice. Indirect laryngoscopy showed normal moving right vocal cord normal mobility and left edematous and immobile. The subglottic space showed e/o ulcerative granuloma. Laryngotracheal involvement is known to occur in upto 16% of patients which may be missed. The involvement may be asymptomatic and range from subtle hoarseness of voice to life threatening stridor. The characteristic lesion is subglottic stenosis. In this present case fibreoptic bronchoscopy revealed left vocal cord and subglottic edema with cord immobility, tracheal narrowing at subarcal level with ulcerative granulomatous lesions.

The condition is fatal if untreated. It is quite often misdiagnosed for tuberculosis in India. Onset of renal involvement may lead to poor prognosis or reduces the chances of recovery. The patient placed on cyclophosphamide and prednisolone which is believed to lead to 95% remission. Laser excision of subglottic stenosis and airway dilatations with silicon and metal stent placement have been tried with guarded prognosis. Laryngo-tracheoplasty for resistant and fixed obstructions would prove a useful procedure in selected cases.

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References


