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GRANULOMATOSIS WITH POLYANGIITIS: A REPORT OF FIVE CASES

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ABSTRACT Granulomatosis with Polyangiitis (GPA) is an autoimmune multi-system disease characterized by necrotising granuloma formation and widespread vasculitis. The clinical manifestations of GPA are diverse enough to behave as a great mimicker. Besides it has such a high mortality, that early detection of GPA is mandatory. We describe 5 such cases of GPA with different clinical presentations, severity of disease and management outcomes.

KEYWORDS : Granulomatosis With Polyangiitis; Chronic Otitis Media; Facial Nerve Palsy; Pulmonary Nodules; Nodular Scleritis.

INTRODUCTION

In 1931 Klinger published a report of a patient with nasal destruction and uraemia who had been found at autopsy to have diffuse granulomata, glomerular lesions and arteritis[1]. However, Friedrich Wegener ultimately characterized the disease through clear delineation of the clinical and pathologic features several years later in 1936 [2]. In January 2011, the Boards of Directors of the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism recommended that the name Wegener's Granulomatosis be changed to Granulomatosis with Polyangiitis, abbreviated as GPA [3, 4]. GPA is an Anti-Neutrophil Cytoplasmic Antibody (*ANCA*) related vasculitis which usually presents as a triad of airway necrotising granulomas, systemic vasculitis and focal necrotising glomerulonephritis. Although GPA is a systemic vascular condition, initial presentation may involve only head and neck symptoms, which are observed in up to 95% of patients [4]. These include rhinosinusitis, epistaxis and sensorineural hearing loss. Various other manifestations such as cutaneous vasculitis, digital gangrene, neurological involvement and even inflammatory polyarthritis have been described, though are not so common. Such diverse clinical presentations make a diagnosis of GPA very difficult at times, as it also mimics various other common disorders like tuberculosis, sarcoidosis and malignancies. In an attempt to further increase the awareness of GPA amongst the medical fraternity, we hereby report five such cases of GPA.

CASE 1

A 25-year-old woman with no relevant past medical history or known co-morbidities presented with complaints of insidious onset deep-seated ear pain, serous ear discharge and loss of hearing in both ears for the past three months. Generalised weakness, polyarthralgia, low grade fever and nasal stuffiness preceded the ear symptoms. A week later she developed bilateral redness and congestion of the eyes with no visual deficit. Subsequently she noticed inability to close both the eyes and drooling of saliva from the angle of mouth bilaterally. Since last four weeks she had also developed hoarseness of voice, cough productive of mucoid sputum and breathlessness on slight exertion. She had no complains suggestive of bowel or nephro-urological symptoms. On examination, her vital signs were stable except for sinus tachycardia. Episcleritis and limbic keratopathy of both eyes was noted. Otological evaluation showed bilateral large central tympanic membrane perforations with evidence of right sided severe mixed hearing loss and left sided moderate conductive hearing loss. She had findings suggestive of gross bilateral infranuclear facial nerve palsy (FNP) whereas examination of other cranial nerves was essentially normal (Fig. 1). Chest examination revealed bilateral inspiratory crackles and wheeze in the infrascapular areas. Laboratory investigations revealed thrombocytosis (5.6 lacs/cu.mm) with a high erythrocyte sedimentation rate (120 mm/1st hour). Biochemical parameters showed normal liver and renal functions. Urinalysis showed no evidence of casts, RBC or proteins. Chest roentogram and CT chest showed extensive pulmonary nodular cavitary lesions. NCCT of the temporal region was suggestive of bilateral cholesteatoma with coalescent mastoiditis and chronic otitis media. Fibreoptic bronchoscopy revealed a solitary nodule in the left main bronchus. Human immunodeficiency virus, hepatitis B and C, and ANA serology were negative. High titres of anti-proteinase 3 along with the above findings concluded a final diagnosis of GPA with extensive head, neck and pulmonary involvement. She was managed with high dose pulse methylprednisolone and intravenous Cyclophosphamide (CYC) therapy along with supportive measures to which she showed some improvement. However within 2 weeks of initiation of treatment she had a downhill course with development of diffuse alveolar haemorrhage culminating her fatal outcome.

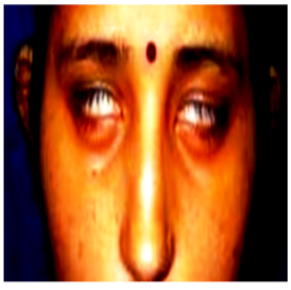

Fig. 1: Bilateral facial nerve palsy in a case of GPA

CASE 2

A 35 year-old woman with presented with non-specific symptoms of low grade fever and easy fatigability of 3 months duration, followed a month later by erythematous rashes over the lower limbs. She then developed pain and blackish discoloration of the left hand digits. Physical examination showed palpable purpura in lower limbs (Fig 2A) and digital gangrene in the left hand index finger (Fig.2 B). Chest X-Ray and CECT chest were normal. Urinalysis revealed numerous red blood cells casts with sub-nephrotic range proteinuria (900 mg/ 24 hours). Her serological tests were strongly positive for C-ANCA (98.8 IU). A renal biopsy showed evidence of pauci-immune crescentic nephritis with focal and segmental necrotizing inflammation along with vasculitis suggestive of GPA. She was managed with pulse Methylprednisolone, injection Rituximab (RTX) and supportive measures. She responded well with a gradual resolution of the digital gangrene.

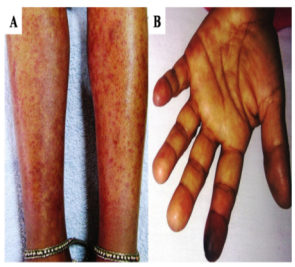

Fig. 2: Vasculitic pupura (A) and Digital Gangrene (B)

CASE 3

A 53-year-old woman presented to our centre with a history of progressively worsening productive cough, shortness of breath and two episodes of streaky haemoptysis. Over the previous 4 months, she had been seen multiple times in outpatient department for symptoms of upper respiratory infections and mild sinusitis. She was exhibited short courses of oral antibiotics and anti-histaminics to which she showed a partial response. She also had complains of polyarthritis involving the small joints of both hands with significant early morning stiffness. She had no other relevant past medical history. A physical examination revealed pallor, tachycardia, hypoxia, tachypnea and pulmonary bilateral fine crackles. An ENT examination was essentially normal. Musculoskeletal examination showed synovitis and tenderness of small joints of both hands. Rest of the general and systemic examination was unremarkable. She was initially managed in the intensive care unit with broad spectrum antibiotics, oxygen support and positive airway pressure ventilation. Laboratory investigations revealed anemia (Hb-9.0 gm/dl), thrombocytosis (6.7 lacs /cu.mm) and raised C-reactive protein levels (40 ng/dl) and positive Rheumatoid factor (55 U/L). Urine analysis was essentially normal. Chest radiograph revealed bilateral multiple cavitatory lesions and consolidation (Figure 3). Her c-ANCA titres were raised (87 U/mL). The above profile was suggestive of GPA with pulmonary and musculoskeletal involvement. A lung biopsy was not feasible in this patient. She was managed accordingly with high dose pulse steroids and intravenous CYC. However within a week of admission she suddenly deteriorated with worsening respiratory distress warranting invasive ventilation, and finally succumbed.

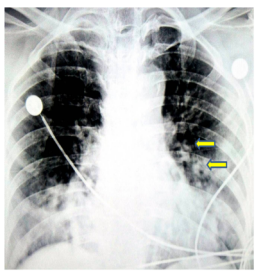

Fig. 3: Multiple cavitary lesions and consolidation

CASE 4

A 45 years old gentleman had presented with recurrent episodes of rhinorrhea, nasal obstruction and crusting, conjunctival congestion and bilateral otalgia of 6 months duration. He had no evidence of respiratory, urinary, neurological involvement or any other constitutional symptoms. Initial evaluation revealed acute rhinosinusitis with congested oropharyngeal mucosa. Laboratory tests done showed raised acute phase reactants and raised c-ANCA levels (77 U/mL). A computed tomography of the chest revealed lower lobe nodular lesions whose biopsy showed necrotising granulomas (Fig. 4). He was then managed as a case of GPA with oral steroids and Methotrexate, to which he showed slight clinical improvement. During the course his treatment he developed rapid onset dysphagia, nasal regurgitation and hoarseness of voice. A neurology consult revealed evidence of lower cranial nerve palsy (IX and X). He was immediately started on pulse CYC and Methylprednisolone therapy along with supportive antibiotics and Ryle's tube feeds. He gradually responded with resolution of dysphagia and dysphonia.

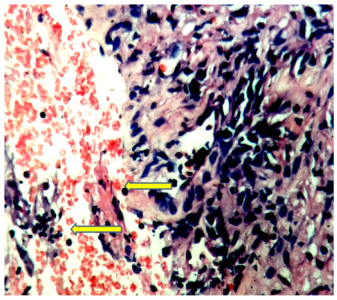

Fig. 4: Haematoxylin and Eosin, 400 X Histopathology of lung biopsy specimen showing necrotising vasculitis

CASE 5

A 44 years old lady with no significant past medical history presented with complaints of ocular congestion, nasal blockage and rhinosinusitis of 02 months duration. She was on over the counter medication for the same till she reported with progressively increasing dyspnoea on exertion, cough productive of mucoid sputum and occasional streaky hemoptysis. On examination her vitals were normal and had normal chest findings. An ocular examination showed nodular episcleritis (Fig. 5A). Chest X-Ray was normal; however, a contrast enhanced computed tomography chest done revealed a nodular lesion in apico-posterior segment of left upper lobe (Fig.5B) and a thick walled cavitatory granuloma in the right lower lobe (Fig. 5C). In view of a strong clinical suspicion of vasculitis, cANCA and pANCA testing was done which was negative. She then underwent a CT guided tissue biopsy from the pulmonary nodule which showed necrotising vasculitis confirming a diagnosis of GPA. She was managed with pulse methylprednisolone and Injection RTX to which she responded well. She was then continued on maintenance remission with oral steroids and mycophenolate mophetil therapy.

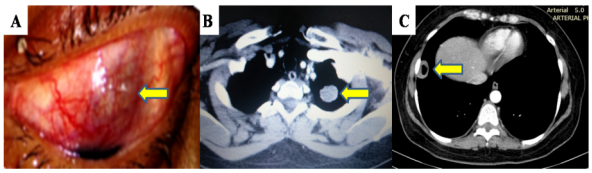

Fig. 5: Nodular scleritis (A); Pulmonary nodule in left lung (B); and cavitatory granuloma in right lung (C)

DISCUSSION

GPA is a rare multisystem autoimmune disease with an annual incidence of 5 to 10 cases per million [3] and is characterised by its predilection for the respiratory tracts and kidneys. The hallmark features include necrotizing granulomatous inflammation and pauci-immune vasculitis in small- and medium-sized blood vessels [2]. Limited form of WG is with involvement of the upper respiratory tract and the lungs with renal sparing [4]. There are no diagnostic criteria for GPA and diagnosis is based on a combination of the clinical manifestations of systemic disease which suggest a diagnosis of vasculitis; positive ANCA serology and histological evidence of necrotising vasculitis, necrotising glomerulonephritis or granulomatous inflammation from a relevant organ biopsy, such as the lung or kidney. It is prudent to note that positive ANCA serology is not always essential for the diagnosis of GPA if the clinical and histological findings are indicative enough. Caution should also be taken in interpreting false positive ANCA serology in patients who do not have any overt clinical or biopsy evidence of GPA. There is obviously a strong and specific association with GPA with cANCA [5], however in up to 10% patients *ANCA* can be negative as seen in case number 5 wherein histopathologic examination of lung nodule was finally conclusive.

The spectrum of organ involvement in GPA ranges widely from head to toe. Otological manifestations may occasionally be the first and only sign of GPA and they are commonly misdiagnosed as infectious or allergic in aetiology as seen in our cases [6]. These include sinusitis, otitis media and hearing loss. Sinusitis is the most frequent initial presentation in about 50-75% of patients with GPA [6, 7]. The inner ear disease causes sensorineural hearing loss (8%), vestibular dysfunction or both, and the proposed mechanisms are the deposition of immune complex in the cochlea, granulomatous compression of the cochlea and vasculitis of the vasa vasorum and cochlear vessels [7, 8].

Ocular manifestations have been reported to occur in patients with GPA. 8-16% of patients may have ocular manifestations as initial presentation. Overall 28 to 58% of patients with GPA have ocular involvement [9]. They can manifest as conjunctivitis, keratitis, scleritis, episcleritis, nasolacrimal duct obstruction, uveitis, retroorbital pseudotumor with proptosis, retinal vessel occlusion, and optic neuritis[9]. Visual loss has been reported in as many as 8% of patients. Hence a complete ophthalmologic examination is an important part of the diagnostic evaluation. 2 of our cases had ocular involvement in the form of episcleritis and nodular scleritis.

Cutaneous involvement such as leucocytoclastic vasculitis, digital infarcts, purpura, ulcers and gangrene occur in GPA [10,11]. They are not pathognomonic, but at times do contribute to a clinical diagnosis of GPA. As seen in one of our cases these features led us to a diagnosis of GPA who had ab initio presented with only non-specific complaints. Without treatment, ischemia and gangrene can progress and lead to significant disability. Therefore, it is important for clinicians to be aware of this rare manifestation and institute early treatment as indicated.

Pulmonary involvement is one of the cardinal features of GPA. It occurs in 87% during the course of the disease and 45% of patients at presentation [12], as seen in 4 out of the 5 cases presented. Cough, pleuritis and hemoptysis are the most common pulmonary symptoms. Most common radiographic image findings in patients with pulmonary involvement include pulmonary infiltrate (67%) and nodules (58%). Lung nodules are the most common manifestation of GPA and occur in approximately 40–70% of patients [12, 13]. The size of GPA nodules varies, most commonly measuring between 2 and 4 cm but ranging from a few mm to 10 cm [13, 14]. Nodules in GPA may occur in a centrilobular distribution, mimicking tuberculosis, hypersensitivity pneumonitis, or an acute viral, bacterial, or fungal pneumonia. Not surprisingly, 2 of our cases had already been subjected to few days of empirical anti-tubercular therapy before GPA was diagnosed. One patient was also detected to have evidence of a solitary bronchial nodule characteristic of GPA.

Musculoskeletal manifestations occur in 30%–50% of the patients with GPA. The most common include myalgia, polyarthralgia, and even inflammatory arthritis [15, 16]. Arthritis in GPA is most commonly associated with large joints, particularly the knees and the ankles. Hoffman et al. [15] reported 44% joint involvement whereas Rodrigues et al. [16] reported 25% musculoskeletal symptoms in the initial presentation of GPA. GPA has been also shown to mimic seropositive rheumatoid arthritis [17] as seen in our 3rd case.

Central neurologic manifestations of GPA include headache, cranial neuropathy, external ophthalmoplegia and Horner syndrome [18]. Cranial neuropathy is the most common CNS manifestation as seen in case number 4. FNP is an extremely rare manifestation of GPA and is considered secondary to compression of the nerve in the middle ear, especially in the presence of a dehiscent fallopian canal or due to vasculitis of its microvasculature [19]. Literature reveals FNP to be present in about 5% of patients alone or in combination with hearing loss, and rarely, may be the presenting feature [18, 19]. A unilateral FNP is described in only 22 cases [20, 21] and only 5 cases of bilateral FNP have been reported in literature as a result of GPA [19-22]. Our first case to the best of our knowledge seems to be another, but extremely rare one with bilateral makes it a unique case of GPA.

The long-term survival in patients with GPA has improved dramatically since the addition of CYC and RTX to the therapeutic regimen [23]. 3 of our cases responded well to either of these 2 drugs. A retrospective analysis had found that annual in-hospital mortality rates among patients with a primary discharge diagnosis of GPA declined by 73 percent, from 9.1 percent in 1993 to 2.5 percent in 2011 [24]. The major causes of death are complications from immunosuppressive therapy, and the underlying disease like renal and pulmonary failure [25], the latter being the cause in 2 of our cases. Untreated patients have a 90 percent mortality rate within two years.

To conclude, GPA is a rare disorder whose varied phenotypic expression makes it one of the greatest masqueraders in clinical medicine. Due to involvement of multiple organ systems, it is not uncommon for patients to report to different clinical specialists as seen in our cases. Besides, a lack of awareness of this entity amongst the general practitioners further contributes to a diagnostic delay. Thus maintaining a high index of suspicion for GPA is mandatory for physicians to make an early diagnosis which significantly reduces the morbidity/mortality associated with this potentially devastating autoimmune disease.

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