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Early Evaluation of Granulomatosis with Polyangiitis (Wegener's) in the Patients with Atypical Sinusitis: An Introduction to Amir Alam Hospital Recommendation for Early Detection of Granulomatosis with Polyangiitis in Sinusitis

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Abstract

Background: Chronic and Atypical Sinusitis (AtS) is often the initial but frequently neglected presentation of Granulomatosis with Polyangiitis (GPA). These patients are primarily referred to otorhinolaryngology clinics and often receive prolonged antimicrobial medications before gradual development of other GPA symptoms.

Objectives: This study was designed to find the number of patients with sinusitis fulfilling the ACR criteria for diagnosis of GPA (Wegener's).

Methods: This cross-sectional study recruited 23 patients with AtS and 32 patients with Typical Sinusitis (TyS). For every patient a through physical examination focusing primarily on the head and neck region, chest X-ray and sinus roentgenograms in Waters and Caldwell views, Complete Blood Count, ESR, BUN, Creatinine, CRP, c-ANCA, p-ANCA and Urinalysis were done. Histopathologic studies were performed on sinus biopsies in AtS patients.

Results: Chronicity, recurrence and sinus masses are three major factors to make a sinusitis atypical. The most frequent complaint was purulent/bloody discharge from the nose found in 15 (65%) of patients with AtS. The most frequent signs and symptoms in TyS group were posterior nasal drainage and production of phlegm. Radiographic studies found 5 bony masses in the AtS group. One patient with AtS was found to have pansinusitis and a disappeared nasal septum. Chest radiographs of patients with TyS did not show any pathologic finding but in two patients with AtS ring shadows in the base of both lungs and calcified granulomas were detected respectively. Histopathologic study in two patients with AtS showed chronic inflammatory cells, granulomas and necrosis highly suggestive for GPA. In AtS group, ESR was elevated in three female and two male patients. c-ANCA was found to be very high in a male patient with elevated ESR, BUN, creatinine and CBC impairment. Urinalysis showed microhematuria in one patient and the same male patient mentioned above had RBC casts. No patient in TyS group met the ACR criteria of GPA but in the AtS group, three (13%) patients (two female and one male) were found to have GPA according to ACR criteria and yet another three (13%) were highly suggestive to have GPA but did not fulfill the ACR criteria.

Conclusion: Early identification of this high number of patients with GPA, in a limited number of otorhinolaryngological patients confers the advantages of screening and early treatment. Rheumatologic consultation in the treatment of AtS patients is therefore inevitable.

Keywords: Granulomatosis with polyangiitis (Wegener's); Atypical sinusitis; ACR criteria; ANCA; Radiography; Urinalysis

Introduction

Wegener's Granulomatosis (WG) was first described by a German medical student in 1931. Five years later Wegener described the same clinical presentation in three other patients [1]. The exact pathogenesis of WG is still unknown but it is an unusual form of vasculitis which almost always affects the sinopulmonary structures [2]. The peak incidence of the disease is the 3rd and 4th decades of life with a 1:1 male-to-female ratio [3]. A triad of necrotizing granulomas of the upper and lower respiratory tract, glomerulitis and vasculitis constitute the systemic Wegener's. Limited Wegener's is often used when the kidneys are not involved [4].

Nowadays it named as Granulomatosis with Polyangiitis (GPA). We know, it is an Anti-Neutrophil Cytoplasmic Antibody (ANCA) associated vasculitis affecting small and medium sized vessels [5]. When there is suspicion of GPA, search for systemic involvements becomes mandatory. Primary investigations constitute chest radiographs, urinalysis, sedimentation rate and cytoplasmic Anti-Neutrophil Cytoplasmic Antibody (c-ANCA) [6]. c-ANCA is not diagnostic but it is claimed to be highly suggestive for GPA. Histopathologic examination of the involved tissue usually reveals necrotic granulomas with vasculitis [7].

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The most common presenting feature of GPA is the upper airway disease ranging from 84-100% of the cases [8] and sinusitis being present in half to two third of the patients as an initial finding [3]. Nasal symptoms often include congestion, crusting and epistaxis. Continuation of destructive processes often causes saddle nose deformity and chronic nasal crusting [9]. The key to diagnosis is the index of suspicion. This study was conducted to find the potential GPA cases among patients with sinusitis as a primary step for earlier detection of GPA.

Material and Methods

During a one year period patients with AtS were enrolled from one otorhinolaryngology clinic held once a week in the largest otorhinolaryngology hospital in Iran. One TyS patient was randomly selected from the same clinic each session. AtS was defined as one of the following conditions accompanying sinusitis: 1) Recurrent (more than 3 episodes in a season) 2) Chronicity as unresponsiveness to more than three weeks of antibiotic therapy 3) Sinus mass 4) Rhinitis 5) Otitis 6) Orbital cellulites 7) Dacryocystitis 8) Mastoiditis 9) Severe pain in the nose and 10) Pansinusitis. The whole study and procedures in the study protocol are approved by the Institutional Review Board of Tehran University of Medical Sciences. All the tests and clinical evaluations were done free-of-charge for all the patients enrolled in this study and every patient received a copy of his laboratory test results.

After description of the procedures and providing written documents on every aspect of this study including the radiographic examination, patients had all signed a written consent form prior to entrance into this study. The patient underwent a thorough physical examination focusing mainly on head, neck and chest regions. Signs and symptoms which were specifically explored include purulent bloody discharge, painful nasal inflammation, painful oral inflammation, saddle nose deformity, strawberry gingival hypertrophy, epistaxis, hemoptysis, cough, phlegm, dyspnea, stridor, arthritis and palpable petechia and purpura. Then chest X-ray and sinus roentgenograms in Waters and Caldwell views were taken. Laboratory tests included Complete Blood Count (CBC), ESR, BUN, Creatinine, CRP, c-ANCA, p-ANCA and Urinalysis. patients with AtS had also underwent sinus biopsy from a site with the most visible inflammation and/or crusts. Patients were diagnosed to have GPA if ACR criteria were met [10].

Data were gathered and anonymously entered into data sheets using computer assigned codes to each patient. Statistical analysis of the data was carried out by a trained statistician blinded to the patient population.

Results

Twenty-three patients with AtS were identified. Chronicity, recurrence and sinus masses are three major factors to make a sinusitis atypical. Table 1 shows the frequency of different atypicalities in the patients with AtS. The most frequent complaint was purulent/bloody discharge from the nose found in 15 (65%) of these patients. Table 2 shows the frequencies of signs and symptoms in the AtS group. Thirty-two patients with TyS were also studied. The most frequent signs and symptoms in this group were posterior nasal drainage and production of phlegm.

Radiographic studies found 5 bony masses in the AtS group. Three masses were found in the maxillary sinuses, one in the ethmoidal sinus and the remaining in the frontal. Involvement of different sinuses in the AtS and TyS groups is shown in table 3. In addition one AtS patient was found to have pansinusitis and a disappeared nasal septum and in another AtS patient cartilaginous and bony nasal septums were largely displaced in different directions. Chest radiographs of patients with TyS did not show any pathologic finding but in two AtS patients ring shadows in the base of both lungs and calcified granulomas were detected respectively. Histopathologic study of biopsies were either unremarkable or with mild chronic inflammation in all patients with AtS except two in whom chronic inflammatory cells, granulomas and necrosis highly suggestive for GPA were found.

In AtS group, leukocytosis was found in two patients, anemia in three patients and one patient had thrombocytosis. ESR was elevated in three female and two male AtS patients. BUN and creatinine was raised in one patient. CRP was slightly elevated in a female and highly elevated in a male. c-ANCA was found to be very high in the same male patient with elevated ESR, BUN, creatinine and CBC impairment. p-ANCA was high in three female patients. Urinalysis showed microhematuria in a patient found to be normal for other tests and the same male patient indicated above had RBC casts. In the TyS group, five patients had leukocytosis, two female patients had anemia and others were found to be normal in their CBC study. ESR was elevated in four male and two female patients. BUN was raised in three patients while creatinine and CRP were found to be normal in all TyS patients. c-ANCA was slightly elevated in a male patient and urinalysis had no important finding suggestive for GPA in any TyS patient.

No patient in TyS group met the ACR criteria of GPA. In the AtS group, three (13%) patients (two female and one male) were found to have GPA according to ACR criteria and yet another three (13%) were highly suggestive to have GPA but did not fulfill the ACR criteria.

Discussion

Granulomatosis with Polyangiitis (GPA), previously named as Wegener's Granulomatosis (WG) is an Anti-Neutrophil Cytoplasmic Antibody (ANCA) associated vasculitis of granulomatous type with small and medium sized vessel involvement [5]. It has an estimated prevalence of 3 per 100,000. Involvement of upper airways occurs in 95% of patients with GPA during the course of the disease and sinusitis being present in half to two third of the patients as an initial finding [3].

Atypicality	Frequencies (Percentages)
Recurrent	8 (35%)
Chronic	8 (35%)
Sinus mass	8 (35%)
Orbital cellulites	5 (22%)
Rhinitis	4 (17.5%)
Pansinusitis	3 (13%)
Dacryocystitis	1 (4.5%)
Severe pain in the nose	1 (4.5%)

Table 1: The frequencies of different types of atypicalities in the atypical sinusitis (AtS) group.

Sign and Symptom	Frequency (Percentages)
Purulent bloody discharge	15 (65%)
Phlegm	14 (61%)
Cough	5 (22%)
Dyspnea	4 (17.5%)
Epistaxis	3 (13%)
Painful nasal inflammation	2 (9%)
Painful oral inflammation	1 (4.5%)
Saddle nose deformity	1 (4.5%)
Stridor	1 (4.5%)

Table 2: The frequencies of different signs and symptoms in AtS patients.

	Maxillary Sinus	Frontal Sinus	Ethmoidal Sinus	Sphenoid Sinus	None
Atypical Sinusitis (AtS)	18 (78%)	9 (39%)	7 (30%)	6 (26%)	2 (9%)
Typical Sinusitis (TyS)	15 (47%)	4 (12.5%)	3 (12.5%)	- (0%)	15 (47%)

Table 3: Involvement of Sinuses in AtS and TyS patients.

It was formerly universally fatal after the onset of renal manifestations but with new treatment regimens the prognosis of GPA is excellent especially if treated before renal involvement [2]. All these bring to mind the importance of early detection which is the cornerstone and the importance of this study. Identification of 3 patients with GPA and still a high probability in 3 others to develop GPA over time, which requires follow-up visits, in a limited number of patients is important by itself not to mention the advantages if confers with early treatment.

GPA is characterized as an ANCA-associated small vessel vasculitis but the importance of ANCA is debated and it is not required to make a diagnosis of GPA by either the ACR or the Chapel Hill Consensus Conference (CHCC) definitions [11]. It could only be suggestive of GPA diagnosis. It has also been shown that ANCA titers are misleading and does not show either the activity or the response to treatment in these patients [12]. In our study only one patient with GPA was found to have elevated c-ANCA in the AtS group and yet another in the TyS group. p-ANCA was elevated in three AtS patients one diagnosed to have GPA. These findings once more emphasize unreliability of ANCA alone in early detection of GPA in the patients with sinusitis.

Renal involvement is important in GPA and once present worsens the prognosis [4]. It could be apparent at the time of presentation but the percentages during the course of the disease reaches the percentages of otorhinolaryngological manifestations at time of GPA presentation [3]. It once again highlights the importance of otorhinolaryngological for early detection of the disease. In our studied population only one patient in the AtS group had a urinalysis fitting into the ACR criteria. This low involvement of the renal system shows that screening of AtS patients is worthy for GPA detection.

Major radiological manifestations of GPA include thickening of soft-tissue in the paranasal sinuses and secondary infection, nasal septum and turbinates necrosis and pulmonary infiltration and nodules which may cavitate [13]. Radiological manifestations in chronic bacterial sinusitis largely include soft-tissue thickening and fluid level in acute exacerbations [14]. A cardinal feature of GPA is pulmonary involvement. It occurs in 45% at presentation and 87% during the course of their disease [3]. In the three GPA cases one had pansinusitis and mucosal thickening in all paranasal sinuses with a normal chest radiograph, the other had normal sinus X-rays but showed narrowing and irregularities in the cervical trachea along with ring shadows in the base of both lungs and the last one had sinus mass in the maxillary and ethmoidal sinuses along with fixed pulmonary calcified granulomas. Our findings along with previous reports [15,16] suggest including radiographic studies of sinuses beside the routine chest radiography. Recurrent episodes of nasal crusting and bacterial sinusitis had been reported in Wegener's (GPA) patients with paranasal sinus obliteration [16].

These findings show a considerable number of patients with GPA, present primarily to otorhinolaryngology clinics with complaint of sinusitis. These patients gradually develop other symptoms of GPA [17]. Keeping in mind these initial presentations of GPA, an avid physician should always have an eye on GPA when treating the patients with AtS and a rheumatologic consultation is worthwhile.

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