Refractory Wegener's Granulomatosis: Effect of Rituximab on Granulomatous Bilateral Orbital Involvement

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Wegener’s granulomatosis is a multi-organ systemic disease characterized by granulomatous inflammation, tissue necrosis and variable degrees of vasculitis in small and medium-sized blood vessels. Individual cases present with variable histopathology, with vasculitis and granulomatous disease representing opposite ends of the spectrum. Two patterns of disease involvement were recently described. The classic type is generally characterized by severe widespread disease including renal involvement, requires aggressive treatment and is associated with a high relapse rate. The second type is a limited disease usually associated with a good prognosis, does not require aggressive treatment and is characterized by a high complete remission rate. Differences in outcome between those WG patients with a predominance of granulomatous versus vasculitic lesions were recently reported [1].

While WG may affect the eyes in a variety of ways, orbital masses with granulomatous expression are often the WG lesions most refractory to treatment [2]. We describe a case of limited WG with severe paranasal and nasal involvement resistant to significant immuno-suppressive treatment, progressing to bone destruction and development of bilateral orbital masses. Rituximab treatment induced significant clinical and radiological improvement.

PATIENT DESCRIPTION

A 50 year old man was initially admitted to another hospital in October 2002 because of right-sided headache and dyspnea of 1 month duration and development of right-side deafness and facial nerve palsy 2 days before admission. The patient had a prior history of chronic obstructive pulmonary disease, diabetes mellitus, and morbid obesity treated only with diet and bronchodilator inhalations. Emergency room evaluation had included sinus X-rays, which revealed right maxillary sinus opacification. Laboratory investigations were significant for normocytic normochromic anemia (hemoglobin 11.38 g/L), leukocytosis (15,000/ml), thrombocytosis (600,000/ml), erythrocyte sedimentation rate 100 mm/hour and C-reactive protein 215 mg/L (normal 0–6). On nasopharyngeal examination, a right inferior nasal conchal mass with bloody crusts and evidence of external and otitis media were found. Computed tomography scan of the sinuses demonstrated bilateral maxillary, ethmoid, sphenoid and frontal sinus and right mastoid air cell opacification. Chest X-ray and CT showed small interstitial infiltrates and nodular shadows bilaterally, which were consistent with Wegener’s granulomatosis.

Biopsy of the nasal mass showed necrotizing granulomatous vasculitis with Langhans giant cells consistent with WG. Further blood tests revealed positive cytoplasmic anti-neutrophil cytoplasmic antibodies by direct immunofluorescence. There was no evidence of renal involvement.

The patient responded rapidly to daily oral cyclophosphamide (2 mg/kg/day) and prednisone (80 mg) with trimethoprim/sulfamethoxazole prophylaxis, but 2 months later severe leukopenia developed and oral cyclophosphamide was switched to the intravenous route 750 mg twice monthly. During the next 6 months, his prednisone dose was reduced slowly as his ANCA titers dropped below detectable levels but CRP and ESR remained elevated. Over the subsequent months his symptoms and serology remained quiescent, except for mild headache, slowly progressive partial deafness, recurrent nasal discharge, and mild dyspnea partially relieved by inhaled salbutamol. His prednisone dose was reduced out of concern for its effect on his diabetes and new hypertension, but the cyclophosphamide was continued. Microscopic hematuria was detected along with atypia of bladder epithelial cells, but cystoscopy was negative. Due to increasing concern about his cumulative cyclophosphamide dose, alternative strategies were attempted despite incompletely suppressed disease. In April 2005, cyclophosphamide was...
discontinued, with combined methotrexate (15 mg/week) and azathioprine (150 mg/d) substituted and prednisone (10 mg) and trimethoprim/sulfamethoxazole continued. Only partial clinical and serological improvement was achieved on this regimen. In December 2007, the patient complained of ptosis, redness and pain of the right eye associated with acute visual loss. New CRP and ESR elevations and a rising ANCA titer were recorded. CT demonstrated maxillary sinus involvement with bone erosion of the posterolateral wall of the right maxillary sinus and extension of a mass to the pterygopalatine fossa and orbit via the inferior orbital fissure. The intra/extraconal soft tissue mass involved the eye muscles and retro-orbital fat. In addition, there was perineural spread via the foramen rotundum to Meckel’s cave (cavernous sinus) to the trigeminal nerve [Figure]. After intravenous pulse methylprednisolone 1000 mg/day for 3 days, rituximab (anti-CD20 monoclonal antibody) was administered in four infusions (500 mg each) given at 2 week intervals with concurrent dexamethasone 4 mg and IV cyclophosphamide 500 mg twice a month for 3 months concurrently.

With this regimen, the patient had complete resolution of his symptoms and the WG was in clinical remission for 9 months, maintained successfully with prednisone 10 mg daily, methotrexate 15 mg weekly, azathioprine 100 mg daily and low dose trimethoprim/sulfamethoxazole twice weekly [Figure]. While his inflammation markers normalized (CRP 6 mg/L, ESR 10 mm/hr) for the first time since diagnosis, and CD 20+ B cell count dropped to 0.2 cells/dl, c-ANCA remained positive at a low titer. He subsequently died suddenly, within 24 hours of admission to another hospital, suffering from multiorgan systems collapse after one day of febrile illness.

**COMMENT**

Ophthalmologic manifestations, including both ocular (i.e., involving the globe) and orbital disease, have been reported in 40–50% of WG patients. An orbital granulomatous process is initially present in only about 2% of all WG cases [2]. However, orbital granulomas are the most common form of ophthalmologic involvement later in the disease course, accounting for as much as 45% of cases with ophthalmologic involvement and can be characterized as contiguous, secondary to extension of granulomatous disease from the nasal passages or paranasal sinuses, or focal, arising primarily within the orbit. The distribution of granulomatous masses within the orbit – specifically with regard to location within intraconal or extraconal compartments and extension to the orbital apex and orbital wall erosion – is poorly documented.

Our patient’s WG vasculitis was initially of the limited type, fulfilling the modified American College of Rheumatology criteria. With time, the disease shifted to a progressive, organ-threatening, multidrug-resistant disease, and with orbital involvement, to the granulomatous end of the spectrum of this condition.

It responded to treatment with rituximab. Rituximab is a chimeric monoclonal antibody directed against the surface glycoprotein CD20, which induces apoptosis in B cells and their depletion in peripheral blood, with B cell levels usually returning to normal within 6 to 12 months. With an important role attributed to ANCA in the pathogenesis of WG, its depletion as a result of decreased B cell level has provided the rationale for the use of rituximab in the treatment of refractory cases of this condition. There are no randomized controlled trials, though, to support its use in WG; the data available until now are based on case reports or case series and three prospective open-label trials [3-5]. In these, good response to rituximab was noted, with minimal side effects and infrequent relapses. The granulomatous form of WG, however, was found to be more resistant to rituximab than the more vasculitic form [3].

The patient reported here presented a predominantly granulomatous manifestation of WG and yet had a good initial response to treatment with rituximab, without side effects. While the results in this and other cases are encouraging, many issues surrounding this form of treatment remain unresolved: such as the time to onset of improvement after rituximab infusion, the duration of remission, the protocol for repeat infusions, and the long-term outcome. Furthermore, the

Coronal CT reconstruction images showing intraorbital soft tissue mass: retro-orbital, intra and extraconal bilateral involvement. [A] Before rituximab treatment, [B] After rituximab treatment
In the case of WG presented here, rituximab treatment resulted in significant clinical and radiological improvement in a patient otherwise intractable to therapy. Rituximab appears to offer therapeutic promise in granulomatous retro-orbital or sinus masses when other treatments are precluded or unsuccessful.

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Role of concomitant therapies needs to be considered. In fact, the reported use of rituximab has been in association with other immunosuppressive medications, either as maintenance of the previous ones or as adjuvant therapy to prevent development of antibodies against rituximab. As the role of rituximab as monotherapy is still uncertain, as in our patient reported here, it was felt that concomitant therapy might enhance the response of this granulomatous form of WG to rituximab. In addition, the significance of c-ANCA persistence in this case, despite depletion of B cells and the absence of symptoms, still needs to be elucidated.

**Capsule**

**A mechanism of crossover in the Y chromosome implicated in diseases**

Theory predicts the chipping away of the male Y chromosome owing to the fact that, for the most part, it has no recombination partner during meiosis, the sexual form of cell division. But male-specific genes on the Y persist, protected in part by palindromic DNA repeats that are maintained through recombination events between each other. These repeats can also be Y’s Achilles’ heel. Page et al. propose a mechanism by which a crossover event after chromosomal replication links the two copies of the chromosome together at a palindrome, creating a larger, abnormal chromosome. These ‘isodicentric’ Y chromosomes are implicated in sex reversal, Turner’s syndrome and male infertility. In a study of samples from 2380 patients with suspected Y-chromosome defects, the authors identified 51 that were apparently formed by this mechanism.

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**Capsule**

**Cancer-fighting robot introduced**

A miniature crawling robot (ViRob) with the potential to treat lung cancer by performing precise medical procedures inside the human body was recently unveiled at the ILSO-Biomed Israel Conference. The ViRob can navigate and crawl in different spaces within the body, including blood vessels, the digestive tract and the respiratory system. In addition, the robot’s unique structure gives it the capability to move in tight spaces and curved passageways as well as the ability to pause within the body, making this groundbreaking technology ideal for performing minimally invasive medical procedures. “This robot is a major breakthrough in the biomedical industry as it allows doctors to access inaccessible areas in the body with minimal invasion,” said Prof. Shoham from the Medical Robotics lab at the Israel Institute of Technology. “It enables a centralized treatment without scattering materials to unnecessary areas in the body. Unveiling our technology at Israel’s leading biomedical conference positions ViRob as the leading technology in the micro-robots industry for medical use.”

Israel High-Tech & Investment Research

“A fleet of British ships-of-war are the best negotiators in Europe”

Horatio Nelson (1758-1805), English flag officer famous for his service in the Royal Navy, particularly during the Napoleonic Wars. He won several victories, including the Battle of Trafalgar in 1805, during which he was killed.

“Look at life through the windshield not the rear-view mirror”

Anonymous