

Joint and Bone Manifestations in GPA

By Christian Pagnoux, MD, MPH

Not all clinically significant questions have been definitively answered by randomized double-blind placebo-controlled trials. The Hallway Consult department in *The Journal of the Canadian Rheumatology Association* will seek a consensus answer from rheumatologic experts for your difficult questions. Please forward questions for future issues to: katiao@sta.ca.

A 48-year-old man, who is overweight (body mass index [BMI] = 42) and with a long-standing treatment for high blood pressure, consulted for persistent rhinitis, recurrent bronchitides, low-grade fever, and some pain in his finger joints and middle back. These conditions have been awakening him at night, resulting in fatigue for two months.

Examination showed high blood pressure (155/90 mmHg) and normal chest and heart auscultation. He had no sensory or motor deficit and normal deep tendon reflexes. Nasal mucosa was erythematous, but without ulceration. There was no clinically obvious synovitis or joint deformation. Back pain was mid-dorsal, with some stiffness of the dorsal spine, but no elective pain on pressure of any of the spinous processes. Serum creatinine was 243 micromol/L and C-reactive protein (CRP) 135 mg/L. Urine analysis revealed red blood cell casts and proteins 0.7 g/24 hours. Anti-neutrophil cytoplasmic antibodies (ANCA) tested positive, with a cytoplasmic-labelling pattern by immunofluorescence and proteinase 3 specificity by enzyme-linked immunosorbent assay (ELISA).

A computed tomography (CT) scan of the chest (without iodine injection) showed no lung parenchymal involvement but revealed a right prevertebral thoracic lesion (T4 to T6-8), which was neither erosive nor infiltrating (Figure 1). A CT-guided biopsy of the latter lesion was performed; this showed infiltration with mixed inflammatory cells and necrosis of the small vessel walls, but no germ or malignant cells. The patient also underwent a kidney biopsy, demonstrating segmental necrotizing pauci-immune glomerulonephritis, further supporting the diagnosis of granulomatosis with polyangiitis (Wegener's syndrome, now GPA).

Granulomatosis with polyangiitis (Wegener's syndrome, now GPA) is one of the three anti-neutrophil cytoplasmic antibodies (ANCA)-associated small-sized vessel vasculitides, even though 20% to 40% of the patients are ANCA negative. There is no epidemiologic data on GPA available to date in Canada, but its annual incidence rate is five to 10 per million habitants, with a prevalence of around 50 to 90 cases per million in European countries that share the Canadian latitudes. Whereas ear, nose and throat (ENT; serous otitis, crusting rhinitis, erosive sinusitis, nasal septum perforation, saddle-nose deformity), kidneys (pauci-immune glomerulonephritis) and lungs (nodules, often excavated, alveolar hemorrhage) are the main target organs, joint manifestations are also within the wide gamut of other potential GPA clinical manifestations.

Clinical Joint and Bone Manifestations in GPA

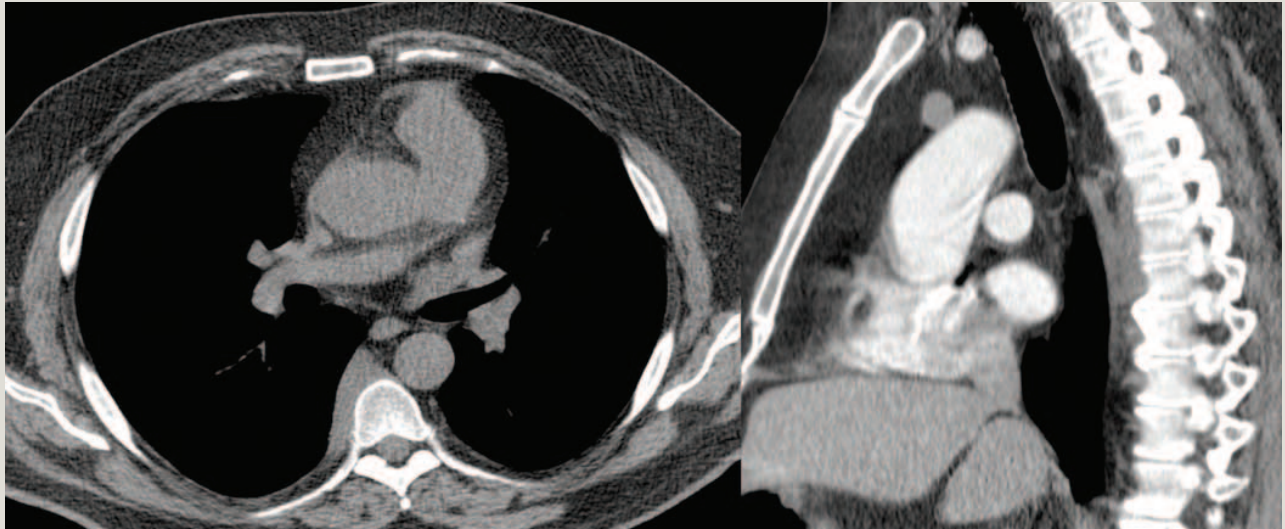
Arthralgias are present at diagnosis or in disease flares in 50% to 70% of the patients with GPA. Polysynovitis

and/or non-erosive polyarthritides (mainly wrists, fingers, knees and/or ankles) are not infrequent during flares, but to a lesser degree (generally fewer than 10% of patients, but up to 30% in one study). These joint manifestations can precede other more specific and/or suggestive manifestations of the disease. Rheumatoid factor (RF) can be detected in 37% to 50% of GPA patients, while anti-cyclic citrullinated peptide (anti-CCP) antibodies very rarely occur. The diagnosis can be challenging, however, at least during the first months after disease onset.

Other possible joint or bone manifestations are more exceptional; these may include prevertebral lesions, like those of the case study patient, or periosteal new bone formations, which are very rare and occur almost exclusively in the tibia(s) and/or fibula(s). Characteristics of these prevertebral lesions are listed below:

- they are usually dorsal;
- they can extend laterally to the prevertebral pleural spaces and/or anteriorly to the middle mediastinum;

Figure 1



Horizontal and reconstructed right parasagittal CT-scan images of the chest of the case-study patient. Para- and prevertebral thoracic T4 to T8 lesion.

- for an unknown reason, they are predominantly right-sided;
- they may be asymptomatic or cause non-specific and, usually, moderate dorsal pain; and
- they have not been reported to lead to compression of nearby structures.

When a computed tomography (CT) scan-guided biopsy is done, granulomatous inflammation, and more rarely, vasculitis, may be seen. The differential diagnoses to rule out mainly include infections, especially tuberculous spondylodiscitis, but also neoplastic diseases and other granulomatous diseases (*i.e.*, sarcoidosis, isolated inflammatory pseudotumor or histiocytosis). Imaging studies, especially magnetic resonance imaging (MRI), can be helpful to exclude spondylodiscitis.

Treatment Options

The treatment of GPA patients with severe manifestations, such as kidney involvement, is well established and codified. Patients must receive a combination of corticosteroids, usually starting with intravenous (IV) pulses of methylprednisolone (7.5 to 15 mg/kg/d for one to three consecutive days), then oral prednisone (1 mg/kg/d for two to four weeks, then progressively tapered), and cyclophosphamide (orally at the dose of 2 mg/kg/d, or with serial IV infusions of 750 mg/m² or 15 mg/kg every two weeks for one month, then every three weeks). Doses

of cyclophosphamide should not exceed 200 mg/d orally or 1,200 mg per IV pulse, and are to be reduced by 25% when glomerular filtration rate is < 25 mL/min or the patient is 75 years or older. Plasma exchange should also be considered in those patients with severe renal disease and/or alveolar hemorrhage; the ongoing Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis (PEXIVAS) trial is aimed at better determining whether plasma exchange is effective in such patients. As soon as remission is achieved, usually around four months after starting induction therapy, patients can be switched to a less toxic maintenance treatment. Using cyclophosphamide to treat newly diagnosed GPA patients at the recommended dosage and schedule, for no longer than necessary to enter remission, is not associated with the major risk of long-term adverse events (*e.g.*, bladder cancer, lymphoma) that have been reported in earlier studies where induction treatments lasted years and cumulative doses often exceeded 35 g. The risk of cyclophosphamide-induced hypofertility or sterility depends on patient's age and cumulative dose, with concerns essentially when the dosage is greater than 10 g to 20 g.

For maintenance therapy, cyclophosphamide is replaced by either azathioprine (2 mg/kg/d) or methotrexate (20 to 25 mg/week). The drugs were shown to be equally effective

and safe in maintaining remission, but renal insufficiency may increase the risk of methotrexate-related toxicity. The optimal duration of maintenance therapy remains unknown, but clearly must not be shorter than 18 months. Ongoing studies may help to better determine the treatment duration, possibly based on individual patient characteristics.

Granulomatous lesions, such as orbital tumors or lung nodules, may respond more slowly to conventional cyclophosphamide therapy; these lesions may also become fibrous but remain unchanged in size as non-active scars, and thus not require the continuation of induction treatment. As such, prevertebral masses often remain unchanged under therapy and intralesion calcifications can appear as a hypothetical scarring process.

Rituximab has recently been shown as effective and safe (at six months) as cyclophosphamide to induce remission in GPA patients, and was just approved in the United States by the U.S. Food and Drug Administration (FDA) for those patients with severe forms of the disease, in combination with corticosteroids. It is not yet approved for treatment of vasculitis in Canada, but may be soon. Whatever the decision of Health Canada will be, in my opinion and for most of the vasculitis experts across the world, rituximab use in GPA should, for the moment, be limited to those patients with severe disease, who are refractory, multi-relapsers and/or have contra-indication(s) to more conventional treatments (*i.e.*, cyclophosphamide, given according to the recommended regimen). Which maintenance treatment should follow rituximab-based induction is not yet determined; ongoing and

planned studies will examine this point using either rituximab re-injections, systematically or based on CD19 T-lymphocyte count, or azathioprine. As for other biologics or diseases treated with biologics, patients receiving rituximab should ideally be entered into longitudinal observational studies or registries. One such registry is under development under the aegis of the recently created Canadian Vasculitis Network (<http://www.canvasc.ca>).

Conclusion

The case-study patient, mentioned above, received a conventional treatment combining corticosteroids and cyclophosphamide for four months, and was subsequently switched to azathioprine for maintenance. His kidney function and systemic manifestations, including finger joint pain, rapidly improved. The prevertebral mass size did not significantly change on a repeat CT scan at six months, but the back pain lessened and no longer required pain medications.

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Dr. Christian Pagnoux was schooled in Paris, France, and specialized in internal medicine. He consulted and was vice-president of the French Vasculitis Study Group for 10 years. Since June 2010, he has worked in the Division of Rheumatology at Mount Sinai Hospital, in Toronto, Ontario. He also participated in the creation of the Canadian Vasculitis Network (CanVasc) with colleagues from across Canada.

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