Small-Vessel Vasculitis in Granulomatous Giant Cell Arteritis

Granulomatous giant cell arteritis (GGCA) (Horton disease) can damage all medium and large arteries. Clinical manifestations are found fundamentally in branches of the carotid artery, and it is currently accepted that the aorta and its main branches are always affected, although they do not show symptoms.[1] Small-vessel vasculitis is considered exceptional. When this occurs, it is important and sometimes difficult to differentiate it from other types of granulomatous vasculitis. We report a case of GGCA that, along with the typical manifestations of headache, jaw claudication, and loss of vision, also had associated pulmonary, cutaneous, muscular, peripheral nervous system, and cranial nerve effects.

Report of a Case. A 74-year-old man was admitted to our hospital with a 7-month history of headaches and jaw claudication. He then experienced visual field loss in the right eye. He did not recover full vision, and he had an episode of bilateral amaurosis that lasted several hours. Fundus examination results, appraised by an ophthalmologist, were normal. In the following months, he experienced fever, persistent headache, and jaw claudication. Thirty days prior to admittance, he experienced dyspnea. The patient was diagnosed with chronic obstructive lung disease, and treatment began that included glucocorticoids. The systemic symptoms disappeared. Chest radiographs showed no pulmonary infiltrates, and he was released with gradual tapering of treatment medications. Coinciding with the suspension of treatment, the headaches, fever, and jaw claudication recurred along with asthenia, difficulty walking and riding a bicycle, and ankle edema. Because of these symptoms, the patient was admitted to our center.

On physical examination, arterial blood pressure was 130/70 mm Hg, heart rate was 108 beats per minute, and axillary temperature was 37.5°C. Temporal arteries showed no signs of inflammation, but pulse on the left was diminished. The results of cardiac auscultation were normal. The patient had bilateral basal pulmonary crepitant rales and multiple reddish nodular lesions on the skin in the pretibial region that were 0.5 to 1 cm in diameter and slightly painful. In addition, there was symmetrical motor weakness in the extremities and a temporal hemianopsia in the right eye. Fundus examination results were again normal.

On admission, laboratory studies disclosed the following values: hemoglobin level, 97 g/L; red blood cell count, 3.5×10^{12}/L; hematocrit, 0.29; platelet count 529×10^{9}/L; erythrocyte sedimentation rate, 103 mm/h; coagulation factor I (fibrinogen), 24 µmol/L; creatinine level, 75 µmol/L (0.8 mg/dL); urea nitrogen level, 13 mmol/L; protein (total), 55 g/L; γ-globulin concentration, 12 g/L; serum iron level, 2.3 µmol/L (13 µg/dL); and serum ferritin level, 195 µg/L. The C3 and C4 complement levels were normal. Test results for antinuclear antibodies, anti-DNA antibodies, and antiglomerular basement membrane antibodies were negative. The level of antineutrophil cytoplasmic antibodies was normal, rheumatoid factor level was 56 IU/mL, and test results for proteinuria were negative at 24 hours; the patient had normal urine sediment. Results from serologic tests for *Brucella*, syphilis, *Borrelia*, and hepatitis B and C viruses were negative.

Alveolar condensation of the upper right lobe was noted on chest x-ray films, and a computed thoracic tomographic scan showed that it was bilateral. Fiberoptic bronchoscopy was done, and the microbiological and cytological study results of the biopsy samples were normal. An electroneurogram was performed that showed signs of peripheral neuropathy with axonal destruction that was predominant in the lower extremities. Since there was a strong suspicion of GGCA, a biopsy was performed on the left temporal artery. The wall was swollen, and there was hardly any vascular opening and considerable inflammation. The intima was swollen as a result of fibrosis, and there was high fibroblastic activity. The internal elastic lamina was fragmented with giant cells into a multinucleated foreign body. The medium was totally disorganized with inflammatory granulomatous infiltration. The adventitia was notably swollen as a result of fibrosis. There was no fibrinoid necrosis or eosinophilic infiltration. Results of a biopsy of the muscle showed discrete inflammatory lymphomonocytoid infiltration in a septal vessel with a loss of wall architecture. The biopsy of a cutaneous lesion revealed an infiltration of multinucleated giant cells, some with a nonidentified phagocytic material.

With the diagnosis of GGCA, the patient was treated with deflazacort, 60 mg. After this treatment, the cutaneous lesions and all of the symptoms progressively disappeared, except for the visual field loss. Two months after being released and treated with deflazacort, 60 mg, the patient's headaches recurred; shortly thereafter, acute dysphonia and dysphagia appeared, and there was discharge of ingested liquids through the patient's nasal orifices. Laryngoscopy was performed and showed evidence of paralysis of the left vocal cord. Velum mobility was normal. Findings of the rest of the neurological examination were normal.

The patient had recovered strength in his lower extremities, and the cutaneous lesions had disappeared. Chest x-ray films, cerebral magnetic resonance imaging, and a Doppler echogram of the carotid arteries were normal. It was determined that the patient had involvement of cranial nerves IX and X caused by arteritis of the

branches of the external carotid artery. Deflazacort therapy was stopped, and treatment with prednisone, 60 mg every 24 hours, and cyclosphamide, 50 mg every 24 hours (later increased to 100 mg every 24 hours), was initiated. With this treatment, the patient's dysphagia disappeared and his dysphonia improved.

Comment. The temporal artery can be affected by different types of vasculitis and occasionally by giant cell arteritis, such as Wegener granulomatosis, Churg-Strauss granulomatosis, and polyarteritis nodosa.[2] Differentiation of GGCA (Horton disease) must be supported by clinical study and histologic testing. In Horton disease, symptoms are usually the result of medium- and large-vessel vasculitis. Our patient, however, had associated peripheral neuropathy with axonal destruction, pneumonitis, cutaneous granulomatosis, and unilateral paralysis of cranial nerves IX and X.

Caselli et al[3] diagnosed 166 cases of GGCA through biopsy; among these, 11 (6.6%) had peripheral neuropathy, 9 (5.4%) had multiple mononeuropathies, and 3 (1.8%) had mononeuropathies. Caselli et al implied that these neuropathies were caused more by vasculitis of the nutrient artery than of the vasa nervorum. A persistent nonproductive cough and a good response to steroid treatment was described in 5% of patients with GGCA.

Descriptions of reticulonodular pulmonary infiltrations, pulmonary nodules, or pleural effusion are less frequent and more recent. In these cases, the diagnosis of polyarteritis nodosa, Wegener granulomatosis, or Churg-Strauss granulomatosis is proposed. However, pulmonary biopsy in GGCA will show a granulomatous vasculitis of the pulmonary arterioles, and venules appear.[4,5] The typical cutaneous manifestation is scalp ulceration located over the temporal arteries. Edema, erythema, bullae, crusts, alopecia, hyperpigmentation, pallor, and livedoid patterns have been described on the skin, but we have not found subcutaneous nodules described that were similar to those seen in our patient.[6]

Two months after beginning steroid treatment, our patient experienced unilateral paralysis of cranial nerves IX and X. The possibility that he had tumoral, inflammatory, or infectious processes near the jugular foramen was dismissed. In GGCA, these manifestations are also related to the inflammation of the external carotid artery branches that irrigate those cranial nerves in the jugular foramen. But an angiogram was not performed for this patient, which could have shown irregularities and arterial narrowing.[7]

Steroid therapy is the treatment of choice for GGCA, and although GGCA is generally considered responsive to steroid treatment, the reality is that remission is not achieved in 46% of patients.[8] In these patients or when it is impossible to completely suppress the use of steroids or if adverse effects result from the use of steroids, other immunosuppressive agents should be considered. It is not clear, however, which of these immunosuppressive agents are the most effective.[9] Treatment with methotrexate and azathioprine seems to be the most useful, but there are no conclusive data regarding the use of cyclophosphamide and cyclosporine to treat GGCA.[10] We treated this patient with cyclophosphamide because we have more experience with its use. We found the response to be good. We conclude that for patients with GGCA, we must look not only for secondary symptoms of the disease in the external carotid and aortic arch branches, but also for systemic manifestations caused by small-vessels. In either case, glucocorticoid therapy is the treatment of choice, combined with methotrexate for selected patients.

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Human Immunodeficiency Virus Testing and Behavior Change

We applaud Freedberg and Samet[1] for their recent contribution and suggestion that physicians lower the clinical threshold for use of human immunodeficiency virus (HIV) testing. They argue that HIV testing should be used for screening purposes rather than solely for diagnosis because testing has 2 advantages: it can help to route infected persons into effective care, and it can help people to reduce their sexual risk behavior. While we agree that these outcomes are desirable and that HIV testing is decidedly beneficial for those who learn that they are infected, we are concerned that the authors are too optimistic regarding the impact of HIV testing on sexual risk behavior.

We recently published a meta-analysis of 27 controlled studies that assessed sexual behavior before and after HIV counseling and testing.[2] The findings indicated that HIV counseling and testing led to risk behavior reduction (eg, decreased frequency of unprotected intercourse) only among HIV-infected people; these results are consistent with the positive expectations of Freedberg and Samet and, indeed, provide substantial public health benefit by reducing the risk of HIV transmission. However, and this is the source of our concern, people

who had negative test results for HIV did not change their sexual risk behavior relative to untested participants. Thus, for the majority of participants (ie, those whose test results were negative), sexual risk behavior reduction was not a compelling rationale for increased HIV testing, at least with counseling as it is typically practiced.

Fortunately, recent evidence suggests that the type of counseling typically delivered can be improved significantly. Evidence for this claim comes from the Centers for Disease Control and Prevention's recent project RESPECT,[3] which tested "typical" counseling (ie, providing HIV information only) against "enhanced" client-centered counseling that was guided by behavioral science theory.[4] The enhanced counseling included conducting a personalized risk assessment and helping the patient to develop a personalized risk reduction plan. Evaluation of this enhanced counseling with patients in sexually transmitted disease clinics indicated that testing supplemented with a 2- or 4-session counseling intervention resulted in significant risk behavior reduction and decreased incidence of recurrent sexually transmitted diseases. Therefore, physicians who hope to use testing to promote risk behavior change among patients who are HIV negative should also plan to use counseling approaches that are based upon behavioral science theory and research to achieve the desired outcomes.

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In reply

We appreciate Weinhardt's comments and support for the idea of changing the paradigm of human immunodeficiency virus (HIV) testing to one of screening rather than diagnosis.[1] We read his recent meta-analysis with interest.[2] With current types of posttest counseling, learning that one is infected with HIV appears to result in safer sexual behaviors. Unfortunately, this is not the case for those who receive results showing they are not infected.[2] We agree that individuals with negative test results for HIV will require the more intensive posttest behavioral counseling that Kamb et al[3] have shown to be effective. This intervention will require an even more substantial commitment of resources than we discussed in our article. That type of commitment, however, may provide significant public health benefit.

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Identifying High-Risk Surgical Patients by Poor Self-Reported Exercise Tolerance

I appreciated the excellent work done by Reilly et al[1] in demonstrating a correlation between self-reported poor exercise tolerance and an increased risk of serious postoperative complications. I want to bring to your readers' and the authors' attention previous work that used a specific activity scale questionnaire[2] to demonstrate this same correlation in a group of patients undergoing major head and neck cancer surgery.[3]

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In reply

We appreciate the comments of Weed and agree that his study examining the relationship between functional status and perioperative complications in patients undergoing otolaryngologic surgery also demonstrates a strong relationship between poor functional status and the development of postoperative medical complications.[1] As in our study,[2] the correlation was strongest for cardiovascular complications.

Our studies differed, however, in their sample size and the breadth of surgical procedures performed. Our study also used a simpler method of assessing exercise tolerance (ie, asking the number of blocks that could be walked or flights of stairs that could be climbed) than the specific activity scale.[3] It has been our concern that busy clinicians are less likely to use assessment scales. A future study comparing the performance of our simple questions and the specific activity scale would be of great interest.

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Overestimation of the Number of Individuals With Hypertension Who Are Eligible for Treatment According to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

In a study by Lloyd-Jones et al,[1] the impact of the recently published *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI)* on the number of subjects with hypertension who are eligible for treatment was estimated. Using data from the Framingham Heart Study, Lloyd-Jones et al estimated that according to the JNC-VI guidelines, 60.6% of the subjects in the high-normal or hypertensive group were eligible for initial drug therapy or were already receiving drug therapy. From the data that were presented in this study, it can be derived that 13.5% of the subjects in the high-normal or hypertensive group were eligible for initial pharmacological treatment.

The main conclusion from the discussion of the limitations of this study is that the number of individuals who are eligible for treatment may have been underestimated. One important limitation that was not discussed by Lloyd-Jones et al was the small number of blood pressure measurements (n=2) on which the classification of the stage of hypertension was based. Using only 2 measurements of blood pressure will lead to a large overestimation of the number of untreated individuals with hypertension, an overestimation that is caused by intraperson variability in blood pressure.[2] In a population-based study in the Netherlands, we estimated that the prevalence of hypertension (diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg or use of antihypertensive medication for the indication of hypertension) may be overestimated by as much as 38% if the small number of blood pressure measurements is not taken into account.[3] Correction for this overestimation is possible by using repeated measurements from a random sample of individuals taken from the entire population.[2] A correction for within-person variability in blood pressure will provide more accurate estimates of the number of individuals who are eligible for treatment and should be taken into consideration in future studies.

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In reply

We are uncertain as to how Klungel and colleagues derived the information that 13.5% of our study subjects in the high-normal or hypertensive categories were eligible for initial drug therapy. As stated in our article,[1] we calculated that 60.6% of these subjects were eligible for initial drug therapy or were already receiving drug therapy. If we consider only untreated subjects, 476 (32.0%) of 1488 fell into one of the following categories for which the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) *recommends initial drug therapy: (1) stage 2 or stage 3 hypertension, (2) stage 1 hypertension in risk group C, or (3) high-normal blood pressure with congestive heart failure or diabetes. These 476 subjects represent 17.0% of all 2794 subjects (treated and untreated with high-normal blood pressure or hypertension).*

We agree that measuring blood pressure twice at a single visit is not an optimal way to categorize subjects into blood pressure stages. Indeed, JNC-VI recommends that patients be diagnosed as having hypertension "based on the average of two or more readings taken at each of two or more visits after an initial screening." However, our estimate of the prevalence of hypertension in our community-based sample is similar to that of the concurrent Third National Health and Nutrition Examination Survey (1988-1991)[2] for subjects age groups similar to ours.

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Thyroid Nodules and Carcinoma in Graves Disease

The article by Cantalamessa and colleagues[1] points out that thyroid nodules occur with a high frequency in patients with Graves disease as determined by ultrasonography and pathological examination findings. Nevertheless, the authors discovered only 1 case of carcinoma among 315 consecutive patients (0.3%), including 106 with nodules. Surprisingly, this is a rather low frequency compared with previous studies and the findings from a recent series.[2] We assume that this low frequency is the result of the fact that only 20 patients underwent surgery.

In our experience, it is difficult to rule out the possibility of carcinoma with certainty without pathological examination.[3] Near total thyroidectomy is still a popular definitive treatment for Graves disease in our country, with more patients undergoing surgery than are treated with radioiodine. In the past 4 years, 115 thyroidectomies were performed at our institution for patients with Graves disease. As summarized in the **Table**, one or more

Results of Pathological Examination of 115 Consecutive Patients Who Underwent Thyroidectomy for Graves Disease*

Age, y	No. of Patients	No. (%) of Patients With ≥1 Nodule
≤45	65	15 (23)
>45	50	23 (46)
Total	**115**	**38 (33)**

*One or more nodules were found in 33% of patients; nodules were significantly more common in older patients (χ^2, P<.001).

nodules were found by pathological examination in 38 patients (33%) and nodules were significantly more common among older patients. In 2 patients (1.7%), papillary carcinomas were diagnosed histologically. Only 1 of these was correctly recognized by fine needle aspiration cytology before surgery. The other was a nondominant 11-mm nodule in a large multinodular goiter (weight, 119 g). Despite its small size, it was considered clinically important because of the presence of an intrathyroidal metastasis. Therefore, radioiodine treatment was introduced.

Our experience supports the findings of other authors. In a large recent series, Chao and colleagues[2] observed that results of fine needle aspiration cytology were positive in only 3 of 13 patients with hyperthyroidism and concomitant carcinoma diagnosed histologically.

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In reply

We thank Čáp and Ryška for their kind interest in our article.[1] As we outlined previously, the available evidence on the risk of thyroid carcinoma for patients with Graves disease is almost exclusively based on pathological studies performed on surgical specimens obtained from patients with Graves disease who have undergone thyroidectomy. The results reported by Čáp and Ryška from the pathological examination of a wide number of patients with Graves disease who underwent thyroidectomy contribute additional data to support the results of previous surgical series.

The study design of our research was quite different. We studied patients with Graves disease who had an ultrasonogram at enrollment and, in the presence of thyroid nodules, were examined with fine needle aspiration (FNA). The patients with benign cytology results were observed for a long period with regular clinical examinations (ultrasonogram and FNA).

In spite of different study designs, our results and those of Čáp and Ryška do not seem considerably discordant. We found 1 case of thyroid carcinoma among 106 patients with Graves disease whose nodules were examined with FNA, while in the series of Čáp and Ryška, 2 of 115 patients with Graves disease showed papillary carcinoma in surgically excised thyroid tissue. Obviously, these numbers are too low to make a reasonable comparison. However, in the series of Čáp and Ryška, in spite of the high frequency of thyroid nodules (33.0% [n=38]), the incidence of carcinoma (1.7% [n=2]) was relatively low. This percentage is clearly lower than that of previous studies on the pathological examination of the excised nodules of patients with Graves disease (22.2% and 45.8%),[2,3] confirming the variable frequency of malignant neoplasms reported in pathological surveys.[3,4]

It was beyond the scope of our study to evaluate the reliability of FNA cytology in the diagnosis of malignant neoplasms of the thyroid. We considered the possible bias represented by false-negative FNA cytology results in our patients with Graves disease and reasonably discarded this hypothesis on the basis of clinical course and regularly performed ultrasonography and FNA examination throughout the long follow-up period (7.0 ± 3.7 years).

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1. Cantalamessa L, Baldini M, Orsatti A, Meroni L, Amodei V, Castagnone D. Thyroid nodules in Graves disease and the risk of thyroid carcinoma. *Arch Intern Med*. 1999;159:1705-1708.
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Hypernatremia in Hospitalized Patients: A Sequel of Inadvertent Fluid Administration

It was intriguing going through the clinical observations of Kahn[1] concerning patients with hypernatremia in association with edema. He described 7 hospitalized patients with hypoalbuminemia and azotemia presenting with increased serum sodium levels and marked edema.[1] In this context, hypernatremia indicates sodium excess in the presence of fluid excess. Furthermore, urine output was increased, implying defective water conservation induced by a lower than expected level of antidiuretic hormone (ADH) activity caused by hypernatremia.[1]

We recently studied a number of hospitalized patients with impaired mental status who developed hypernatremia without marked edema. These patients were divided into 2 groups. The first group consisted of 4 patients who were admitted because of malignant neoplasm–related hypercalcemia. In this setting, isotonic sodium chloride solution together with potassium supplements was administered intravenously to replenish intravascu-

lar volume and restore calcium and potassium levels. The second group consisted of 5 patients who experienced stroke and who received isotonic sodium chloride solution along with mannitol solution (3 of 5 patients).

In all of these patients, serum sodium levels rose from a mean value of 142 mmol/L (range, 139-144 mmol/L) to a mean value of 154 mmol/L (range, 149-160 mmol/L) within 3 days of therapy. At the time of hypernatremia, urine output averaged 1450 mL/24 h (range, 800-1900 mL/24 h) and urine sodium concentration averaged 48 mmol/L (range, 36-65 mmol/L). On physical examination, there was no evidence of extracellular volume alteration (depletion or expansion). In 4 patients (2 from each group), a small increase in total body weight was observed (mean±SE, 1.6±0.4 kg), indicating an inability to normally excrete fluid overload. Hence, our patients developed mildly hypervolemic hypernatremia resulting from insensible losses in combination with the ongoing hypercalcemia- and mannitol-induced renal hypotonic losses coupled with the administration of isotonic or hypertonic solution. In fact, the addition of potassium chloride significantly increases the osmolality of administered fluids (1 L of 0.9% sodium chloride plus potassium chloride, 54 mmol/L, results in an osmolality of 360 mmol/L H_2O). Thus, the concentration of potassium chloride that is administered should be taken into account when calculating the amount of solutes during the correction of electrolyte abnormalities.[2] In accordance with the observations of Kahn,[1] in our patients the activity of ADH may be less than expected for the level of hypernatremia. This defective ADH-induced water conservation leads to an increased water and urine output and may also be related to factors not directly related to hypercalcemia or mannitol administration, such as the associated volume expansion, which tends to inhibit ADH release; stress-induced increased glucocorticoids, which can inhibit osmotically mediated ADH release[3]; stress-induced high epinephrine concentrations, which have been shown to inhibit ADH-mediated water reabsorption[4]; and the diminished glomerular filtration rate that was observed in 3 patients with hypercalcemia.

In concert with Kahn's suggestions, our data indicate that hypernatremia does not result from the loss of water in excess of the loss of sodium. However, it may develop in severely ill hospitalized patients in association with inadvertent excess fluid administration (ie, the replacement of hypotonic losses by isotonic or even hypertonic solutions), particularly when water intake is poor.

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In reply

The interesting patients described by Milionis et al provide further evidence that hypernatremia may not infrequently be associated with normal or increased body water. Others have noted that patients with volume depletion may become overloaded with salt and water for days when given large volumes of fluid containing both salt and glucose.[1,2] The development of hypernatremia in such cases may reflect primarily excessive salt retention, possibly at a site not associated with much water reabsorption, such as the distal convoluted tubule. Less than maximal production and/or action of antidiuretic hormones in this setting may be physiologically appropriate to prevent fluid overload. This condition may be the opposite of that which occurs in cases of hyponatremia with "renal salt wasting," in which antidiuretic hormone levels are high to maintain volume despite low serum osmolality.[3]

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