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Giant cell arteritis: Diagnosing and managing urgent complications of disease and therapy

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Giant cell arteritis (GCA) is one of the most common forms of vasculitis in persons of European and North American descent, with an estimated prevalence of 1/500 in individuals over the age of 50.[1] GCA is a systemic inflammatory vascular disease, most frequently affecting the extracranial branches of the carotid artery. With the advent and increasing use of noninvasive imaging studies, GCA has been recognized to affect the aorta and its primary branches, with vascular involvement similar to what is seen in Takayasu arteritis.[2]

Once the diagnosis of GCA has been established, monitoring patients for disease activity and associated comorbidities of disease and treatment is an essential component of their care. Visual loss, one of the most dreaded complications of the disease, can occur even after the institution of appropriate therapy. Other complications, such as aortic aneurysm, can occur after many years during which time disease activity has appeared clinically quiescent. Awareness of potential comorbid complications of GCA and its treatment is key in early recognition and intervention, which may be organ- and life-saving.

Visual loss in GCA: An ophthalmologic emergency

Visual manifestations of GCA include blurred vision, diplopia, amaurosis fugax, scotoma, and abrupt loss of vision. Visual loss in GCA has been reported in 5%-58% of patients in the pre-steroid era.[3-5] However, since the advent of glucocorticoid use, recent longitudinal cohort studies report permanent visual loss (partial or complete, monocular or binocular) in 5%-15% of patients. The most common etiology of vision loss in GCA is anterior ischemic optic neuropathy; it can also be caused by an occipital stroke or by central retinal arterial occlusion. Factors that are predictive of permanent visual loss in GCA include a previous episode of transient visual loss (RR 6.35) and stroke (RR 7.65).[6] Some cohort studies have suggested that lower levels of acute phase reactants (erythrocyte sedimentation rate and C-reactive protein) and the

lack of systemic symptoms are associated with an increased risk of blindness, but these associations are not universally noted.[7-8]

In patients with GCA who present with visual disturbances or visual loss, glucocorticoid therapy leads to recovery of vision in about one-third of patients who receive therapy promptly (within 24 hours of symptom onset), with no benefit shown in patients in whom therapy was instituted after more than 48 hours following symptom onset. Although patients may develop visual loss while receiving glucocorticoid therapy, this occurs in less than 10% of all patients.

Patients with GCA who present with visual symptoms should undergo ophthalmologic evaluation. Other causes of visual disturbances often seen in GCA, such as cataracts, glaucoma, and central serous retinopathy, are associated with glucocorticoid therapy and would be treated differently than visual disturbances associated with active disease. However, it is important to remember that these conditions can be seen simultaneously in patients with active GCA. Stroke associated with visual disturbances can be identified by computed tomography or magnetic resonance imaging of the brain and cerebral blood vessels.

High-dose glucocorticoid therapy is indicated in patients with GCA who present with visual loss, and should be initiated immediately. Patients are initially treated with intravenous pulse steroids with one gram of methylprednisolone (or equivalent) for 3 to 5 days, then followed by 1 mg/kg of prednisone (or equivalent) in divided doses daily.

Aortic aneurysm and dissection

Prior to the increasing use of noninvasive vascular imaging studies, aortic involvement in GCA was frequently identified at the time of surgery for aortic insufficiency or aneurysm. With increasing use of these imaging techniques, the prevalence of aortic aneurysm and dissection has been increasingly appreciated in this population, affecting ~20% of patients.[2-9] Involvement of the thoracic aorta occurs most commonly. This manifestation of GCA may have serious consequences, with the Mayo Clinic inception cohort demonstrating a median survival of 1.1 years following the diagnosis of thoracic aortic dissection.[10]

Symptoms of thoracic aortic aneurysm may include upper back pain or chest pain, hoarseness (from laryngeal nerve compression), dysphagia, dyspnea, or superior vena cava syndrome. However, many patients are asymptomatic. Patients with aortic dissection often present acutely with pain frequently described as "tearing" in the upper back or chest, hypotension, acute myocardial infarction, stroke, or congestive heart failure. Dissection into the pericardial space may result in pericardial tamponade. On examination, patients may manifest with the murmur of aortic insufficiency, or may have a discrepancy in blood pressure or pulse between the upper extremities. GCA patients with hypertension, coronary artery disease, or hyperlipidemia are at higher risk for developing aortic aneurysm or dissection.[10-12]

The diagnosis of aortic aneurysm or dissection is suspected based on clinical presentation, but confirmed with the use of imaging studies. Chest radiography may demonstrate a widened mediastinum, increased cardiac silhouette (in the case of dissection into the pericardial space) or pleural effusion (if dissection into the pleural space occurs). However, this imaging modality is neither sensitive nor specific enough to establish these diagnoses. Computed tomography imaging is widely utilized because of its widespread availability. Magnetic resonance imaging and multiplane transesophageal echocardiography also are useful imaging modalities but require both advanced technology and trained personnel for study interpretation, which are not as widely available.

As in the general population, ascending aortic dissection in patients with GCA is a surgical emergency. Patients with descending aortic dissections may be treated medically when the dissection is stable, or may require surgical intervention in the setting of hemorrhage or dissection progression. In patients with active GCA, treatment with glucocorticoids should be initiated, but therapy may be delayed in patients who require immediate surgical

intervention. The decision regarding institution of therapy perioperatively should be made in concert with the surgical team to minimize infection risk and issues with wound healing.

Cerebrovascular complications of GCA

Transient ischemic attack (TIA) and cerebrovascular accident (CVA) occur in up to 10% of patients with GCA.[2] Either of these manifestations may be the initial presenting sign of GCA. In the majority of patients with CVA, the carotid and vertebral arteries are the most commonly affected. In fact, vertebrobasilar CVA is seen more often in GCA patients than in age-matched non-GCA patients with CVA. Patients with active disease are more likely to develop cerebrovascular manifestations of GCA from active arteritis, but thromboembolism or extension of a local thrombus may also cause CVA in GCA. Risk factors for CVA in GCA include smoking, permanent visual loss associated with GCA, and hypertension.[13] Two retrospective cohort analyses found fewer cranial ischemic events in patients receiving antiplatelet therapy prior to the diagnosis of GCA, suggesting that this therapy may be protective against TIA and CVA.[14-15] However, prospective studies evaluating the effects of antiplatelet therapy initiated at the time or following the diagnosis of GCA are needed to definitely determine if this protective effect is present if therapy is initiated at this time.

Similar to patients who present with acute visual loss, GCA patients with CVA should receive prompt treatment with intravenous high-dose glucocorticoid therapy. In patients presenting with acute CVA in whom the diagnosis of GCA is suspected, treatment should also be immediately initiated, with a temporal artery biopsy obtained promptly. It is important to remember that the yield of temporal artery biopsy for the diagnosis of GCA decreases following the institution of steroids, with one series reporting positive biopsy findings in over three-quarters of patients undergoing biopsy after treatment for less than two weeks but only 40% of patients treated for more than four weeks.[16]

Visceral ischemia in GCA

Although mesenteric artery involvement is seen in ~10% of U.S. patients with GCA, mesenteric ischemia is a rare complication of the disease.[2] Patients may present with mesenteric ischemia in the absence of cranial symptoms (5/12 patients in one case series), with symptoms including acute persisting abdominal pain, postprandial abdominal pain, anorexia, and vomiting.[17] In this case series, survival was only 50%, with half of the patients requiring bowel resection and treatment with high-dose glucocorticoids.

Treatment-associated emergent complications in GCA

Adverse effects on the central nervous system

Many patients receiving glucocorticoid therapy report central nervous system side effects, such as anxiety, irritability, or insomnia. These side effects are easily managed in the majority of patients. More serious side effects are noted in a subpopulation of patients, with older patients or those receiving higher doses of steroids more susceptible to these adverse effects. One study of 126 patients with GCA over the age of 65 found that 16% of patients suffered psychiatric effects, including mood disturbances, depression, mania, anxiety neuroses, and dementia.[18] In this study, adverse effects generally began during the first month of therapy and were dose-dependent. One-quarter of patients required inpatient care for these adverse effects.

Reduction of steroid dose may be helpful in alleviating psychiatric side effects in GCA. However, for patients in whom steroid dose cannot be reduced because of active disease, or for those in whom steroid dose reduction does not alleviate symptoms, pharmacologic therapy appropriate to the psychiatric manifestation is indicated and has been reported to be efficacious.

Immunosuppressive therapy and infection in GCA

Any immunosuppressive therapy, including glucocorticoid therapy, places GCA patients at increased risk of infection. Patients may develop common community-acquired bacterial or viral infections, but also are at risk for less common infections, including opportunistic infections, such as those seen in patients receiving cancer chemotherapy or in organ transplant patients. In addition, immunosuppressive therapy in GCA has been associated with an increased risk of reactivation of latent infection, including tuberculosis or varicella zoster virus.

Another consideration in patients with GCA receiving immunosuppressive therapy is that the usual signs and symptoms of infection may be altered or absent, especially in patients receiving high doses of glucocorticoids. This means that a high index of suspicion for infectious complications of therapy must be maintained, with a prompt and aggressive evaluation of any new signs or symptoms in patients with GCA. This is less difficult in patients who manifest with focal signs or symptoms, in whom a focused investigation can be easily undertaken, than in patients who present with nonspecific signs or symptoms. In the latter group, or in patients who are clearly systemically ill, an inpatient evaluation with a broad initial focus is indicated, and should include surveillance for both common community-acquired and opportunistic pathogens. Infectious disease consultation is often very helpful, especially for patients in whom common pathogens have been eliminated as the source of infection. Additionally, patients who are systemically ill may also require stress dose steroids to prevent adrenal insufficiency. For patients whose GCA is adequately controlled, decreasing glucocorticoid dose to the lowest dose that maintains disease remission may help facilitate recovery from aggressive infections.

Glucocorticoid therapy and adverse cardiovascular events

Little data is available about the effects of glucocorticoids on the cardiovascular system in patients with GCA. However, data from the general population demonstrates that patients without a history of prior hospitalization for cardiovascular disease receiving 7.5 mg/day of prednisone (or the equivalent) are at increased risk for cardiovascular events, including myocardial infarction, CVA, and congestive heart failure.[19] Furthermore, the risk of events was higher in patients receiving prolonged courses of treatment or high-dose glucocorticoid therapy. Case reports exist of patients suffering severe cardiovascular events, including sudden death, during or after receiving intravenous pulse glucocorticoid therapy.[20] However, in many cases it was not able to be determined whether this was a direct effect of therapy or related to the underlying disorder requiring treatment. Nonetheless, it has been suggested that patients with a history of cardiovascular disease receiving intravenous pulse glucocorticoid therapy undergo cardiac monitoring during treatment.

Awareness and early recognition of GCA-associated morbidities and adverse effects of treatment allows for prompt intervention and may be organ- or life-saving. It is important to remember that the side effects of therapy can occur at any time and can be as serious as adverse effects from disease.

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