Polymyalgia rheumatica and giant cell arteritis

Patients with a past history of the relatively benign condition polymyalgia rheumatica should be viewed as candidates for the development of giant cell arteritis, the major morbidity of which is visual loss that can become permanent if the condition is untreated.

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Polymyalgia rheumatica and giant cell arteritis (also known as temporal arteritis) are well represented inflammatory conditions among the geriatric population. They are associated with a marked systemic inflammatory response and in general respond well to corticosteroid therapy.

Polymyalgia rheumatica and giant cell arteritis share some epidemiological features and some susceptibility genes (particularly *HLA-DRB1*). Both conditions are found in the over-50 years age group, the mean age onset is 70 years and 90% of patients are older than 60 years. There is a female preponderance in a 2:1 ratio. The conditions may occur simultaneously in the same patient, about 10% of polymyalgia rheumatica patients developing giant cell arteritis, and about 30 to 40% of giant cell arteritis patients having polymyalgia rheumatica.

Polymyalgia rheumatica

Untreated polymyalgia rheumatica has a significant morbidity because the disease so dramatically interferes with a person's quality of life. It is, however, a benign condition, being self-limited and tending to settle over a period of 12 to 24 months, and symptoms can be controlled with low dose corticosteroids. While the joint problems of the condition are not associated with progressive joint damage as might occur in rheumatoid arthritis, corticosteroid treatment-related morbidity can be significant and giant cell arteritis may occur (with the risk of visual loss if untreated).

Presentation and diagnosis

The diagnosis of polymyalgia rheumatica remains a clinical one based on the classic picture of new onset early morning stiffness of at least one hour's duration and stiffness after prolonged inactivity (the gel phenomenon). Examination findings of shoulder and/or hip irritability on passive movement are found, along with markedly elevated erythrocyte sedimentation rate (ESR), typically to above 50 mm/h, and/or C-reactive protein (CRP) level. As an acute or subacute illness, patients often report 'suddenly feeling old' or that they feel they have aged quickly. The exquisite responsiveness of symptoms to relatively low doses (15 mg/day or less) of prednisolone (Panafcortelone, Predsolone, Redipred, Solone) adds to the confirmatory picture.

IN SUMMARY

- **Polymyalgia rheumatica and giant cell arteritis are relatively common related inflammatory conditions in people aged over 50 years. The aetiology is unknown.**
- **About 10% of patients with polymyalgia rheumatica develop giant cell arteritis, and about 30 to 40% of patients with giant cell arteritis have associated polymyalgia rheumatica.**
- **Neither condition should be diagnosed in patients under 50 years of age, and polymyalgia rheumatica should not be invoked as an explanation for unilateral symptoms.**
- **Patients with a past history of polymyalgia rheumatica should be viewed as candidates for the development of giant cell arteritis, the major morbidity of which is visual loss.**
- **Giant cell arteritis should be considered in an elderly patient with pyrexia of unknown origin.**

Polymyalgia rheumatica: some differential diagnoses

Rheumatoid arthritis

Polymyalgic symptoms with proximal joint involvement at the hips and shoulders are much more common in older patients with rheumatoid arthritis than in young patients with rheumatoid arthritis, who typically have more distal symptoms affecting the hands and feet. Progression over time to peripheral joint involvement and the presence of significant titres of rheumatoid factor increases the clinical suspicion of rheumatoid arthritis mimicking polymyalgia rheumatica.

A newly defined serological test, anti-cyclic citrullinated peptide (CCP) has been found to be highly specific for rheumatoid arthritis and positive anti-CCP antibodies in a patient suspected of having polymyalgia rheumatica strongly suggests early onset rheumatoid arthritis rather than true polymyalgia rheumatica.

Myositis

While polymyositis is often thought of as an explanation for diffuse muscle pains, typically patients with this condition present with weakness without substantial complaints of pain. A normal creatine kinase level will significantly reduce the probability of polymyositis. Also, irritability upon movements of the shoulder and hip, which are signs typical of polymyalgia rheumatica, is not seen in polymyositis.

Vitamin D deficiency

Patients with vitamin D deficiency, which is an increasingly recognised problem in older populations, may present with diffuse aching and stiffness. Vitamin D levels should be checked in any patient in whom a diagnosis of polymyalgia rheumatica is being considered, not only as a differential diagnostic feature but also to determine the degree of vitamin D supplementation that might be required as prophylaxis against corticosteroid-induced osteoporosis.

Degenerative rather than inflammatory joint problems

Rotator cuff problems are extremely common in the elderly, as are pain referred from the lumbar spine and primary hip disease or periarticular hip problems such as trochanteric bursitis. The presence of diffuse pains coupled with a raised ESR does not in itself prove the presence of polymyalgia rheumatica, and an appropriate clinical picture with prominence of morning stiffness and the gel phenomenon should be sought before considering such a diagnosis.

At times it can be extraordinarily difficult to determine whether an elderly person with diffuse musculoskeletal complaints has an inflammatory joint problem, and a trial of prednisolone 15 mg daily for two weeks may be warranted to resolve the issue. Dramatic resolution of complaints would be expected with such treatment in a patient with polymyalgia rheumatica, and certainly such dramatic resolution would be required to justify the potential toxicity of continuing corticosteroid therapy. A marginal response to corticosteroid therapy should not be seen as supportive evidence for the presence of polymyalgia rheumatica.

While patients may present with initial unilateral involvement in one girdle (shoulder or hip), over a period of weeks to several months it is usual for the condition to become bilateral and affect both girdles. Persisting involvement of one joint is not typical of polymyalgia rheumatica and raises concerns about an alternative diagnosis. Similarly, bilateral onset of shoulder pain does not suggest primary rotator cuff degeneration and would raise the suspicion of a polymyalgic syndrome. Differential diagnoses for polymyalgia rheumatica are discussed in the box above.

Contrary to its myopathic namesake, polymyalgia rheumatica is not a muscle disease and has an underlying pathology of shoulder and hip synovitis and bursitis. This has been shown by magnetic resonance imaging and ultrasound examination of the shoulders, and by shoulder biopsy at arthroscopy. The physical examination correlative is pain with passive and active shoulder and/or hip movement.

Patients with rheumatoid arthritis, particularly those in older age groups, may present in a fashion similar to patients with polymyalgia rheumatica, but with time the more rheumatoid nature of the problem – prominent involvement in the wrists, fingers and metatarsophalangeal joints – almost invariably becomes evident. The younger a patient is with what appears to be polymyalgia rheumatica, the more likely it is that the problem is rheumatoid arthritis with a more proximal (polymyalgic) onset.

Management

Symptoms can be alleviated in most patients with initial daily doses of 15 mg or less of prednisolone or an equivalent corticosteroid, with some patients requiring only 7.5 mg per day. Symptoms can be controlled with NSAIDs in a small proportion of patients, but the clinical impression is that the degree of control with these drugs is not nearly as complete as with corticosteroids. The prednisolone dose that alleviates symptoms should be

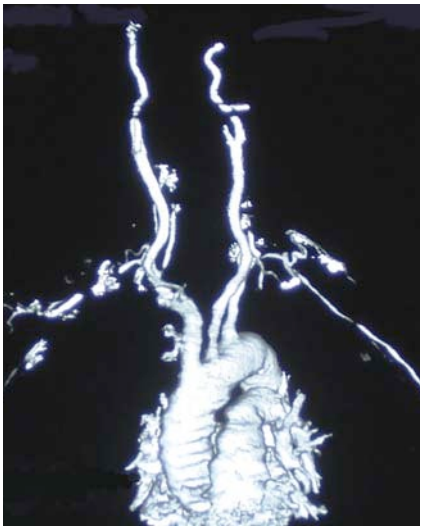

Figure 1. Giant cell arteritis – CT angiogram. The left subclavian artery shows the classic smooth tapered appearance of vasculitic narrowing, and the right subclavian artery, areas of stenoses alternating with normal flow.

maintained for three to four weeks, at which stage the ESR and CRP level would be expected to have normalised. After that, a slow wean is commenced, typically by 2.5 mg every three weeks down to 10 mg, and 1 mg reductions every three to four weeks thereafter. Overly rapid steroid reduction often results in a major exacerbation of pain requiring reinstitution of corticosteroid at a higher dosage than would otherwise be necessary. The dictum of steroid reduction in polymyalgia rheumatica is to reduce by small amounts and to do so slowly – on average, over a period of nine to 18 months.

A challenging aspect of management is to wean patients off prednisolone entirely as pre-existing degenerative complaints such as rotator cuff degeneration can be masked by medium dose prednisolone, often recurring at doses of 5 mg per day or less. It has been shown that a proportion of patients do not cease corticosteroid therapy; however, this probably reflects conservative physician behaviour more than the patient's need to stay on prednisolone. There is no role for long term 'maintenance therapy' in polymyalgia rheumatica in the vast majority of cases. Occasionally, patients do experience great difficulty in coming off prednisolone and it is likely that such cases may represent mild forms of rheumatoid arthritis rather than typical polymyalgia rheumatica. Arguing by analogy from experience with rheumatoid arthritis, randomised trials have evaluated the role of methotrexate in polymyalgia rheumatica. Only small reductions in prednisolone dose were achievable in patients treated with concomitant methotrexate, and overall toxicity was not reduced. Consequently, it has been concluded that methotrexate has no role as routine adjunctive therapy to corticosteroids in polymyalgia rheumatica, although it may be of value in the rare case that is truly resistant to treatment.

Specialist rheumatology management may be required to guide patients through prednisolone withdrawal and to differentiate musculoskeletal complaints arising from other conditions and those resulting from inadequately controlled polymyalgia rheumatica. Once corticosteroid withdrawal is achieved, specialist follow up is usually not required, although patients should be regarded as being at risk of developing giant cell arteritis and its complications, most worryingly visual loss, for the rest of their life.

Giant cell arteritis: some differential diagnoses

While there is a multitude of causes of headache and jaw pain, the principal differential diagnoses for giant cell arteritis are other forms of vasculitis affecting the cranial arteries. These include:

- polyarteritis nodosa
- Wegener's granulomatosis
- Churg–Strauss vasculitis.

Patients with these conditions will present with a clinical picture identical to that seen in giant cell arteritis due to the identical distribution of involvement.

The differential diagnosis should be established on the basis of clinical features outside the distribution of large vessels, such as cutaneous vasculitis (which is not typically seen in giant cell arteritis) and the appearance of polymorphonuclear cells or eosinophils in temporal artery biopsies (which, again, are not typical features of giant cell arteritis).

Giant cell arteritis

Giant cell arteritis is a granulomatous large vessel vasculitis typically affecting only the aorta and its named branches. The most commonly involved arteries are the extracranial vertebral arteries, superficial temporal arteries, posterior ciliary arteries and ophthalmic arteries. The condition is more common in populations of northern European descent than in the general population, and much less common in Asian and African populations. As the risk of permanent visual loss in untreated giant cell arteritis is in the order of 15%, it is important that the diagnosis is not missed.

The spontaneous remission of giant cell arteritis over a two- to three-year period was well defined in the pre-corticosteroid era. The introduction of corticosteroids, however, has dramatically improved the quality of life of patients with the condition and also protects them from possible visual loss.

Presentation

The classic symptoms of giant cell arteritis are:

- new headaches
- visual loss, which in many cases is preceded by temporary visual loss (amaurosis); this visual loss is monocular and often altitudinal, such that people lose the upper half of their visual fields
- new scalp tenderness and sensitivity
- jaw claudication, which, while common, is typically not a presenting feature; a history of it is often only obtained on specific questioning.

Fever is a less common presentation, although giant cell arteritis is now recognised as a cause of about 15% of cases of pyrexia of unknown origin in patients aged over 60 years.

Large vessel disease presentation

Some 10 to 15% of patients with giant cell arteritis develop stenoses of the aorta and its proximal branches. People presenting with a typical aortic arch syndrome often lack symptoms referable to the cranial artery. Patients with large vessel disease presentation are typically somewhat younger than patients with classical cranial giant cell arteritis and have a lower ESR. Upper limb ischaemic symptoms may be subacute, presenting as claudication, or occasionally acute, presenting with critical limb ischaemia. Temporal artery biopsy is not a particularly useful investigation in this group, being positive in only 50% of cases.

The diagnosis is made on angiography, and CT angiography has allowed non-invasive visualisation (Figure 1). In this situation the angiogram allows confident diagnosis and there is no need to proceed to temporal artery biopsy.

Other presentations

Occasionally patients may have a respiratory presentation with sore throat or cough, which is probably due to endobronchial vessel inflammation.

Rare manifestations involve unusual sites of involvement distal to the proximal branches of the aorta. In particular, involvement of the uterus, ovary and cervix and, less commonly, the prostate has been reported.

Up to 1% of patients at necropsy have evidence of giant cell arteritis in the aorta. Most of these patients, however, seem to have been free of symptoms.

Diagnosis

It is imperative that a diagnosis is established beyond reasonable doubt because of the risk of visual loss if giant cell arteritis goes untreated and to avoid treating people unnecessarily with corticosteroids as the risk of complications of this therapy in an older patients is about 30 to 40%. Differential diagnoses for giant cell arteritis are discussed in the box on page 48.

The diagnosis is suggested by the clinical picture, and reinforced by simple laboratory tests. Full blood examination typically finds mild anaemia of chronic disease, often with thrombocytosis. Liver function tests often show rises in alkaline phosphatase and gamma glutamyltransferase levels. The critical blood tests are those reflecting inflammatory reaction – that is, ESR and CRP level. It is usual for both to be abnormal in untreated giant cell arteritis; generally the ESR is above 50 mm/h and the CRP is above 40 mg/L.

The gold standard for diagnosis of giant cell arteritis is a positive temporal artery biopsy. Obtaining longer biopsy specimens (at least 3 cm in length) improves the diagnostic yield as the condition is segmental with areas of involvement as short as 0.4 mm alternating with areas without any disease. Obtaining bilateral biopsies increases the diagnostic yield up to 15%. Due to the concern of visual loss, it is prudent to commence corticosteroid therapy immediately the diagnosis is considered, prior to biopsy. Although biopsies have been reported positive up to six months after corticosteroid initiation, obtaining a biopsy as soon as possible is preferable, generally within one to two weeks being a practicable goal.

The biopsy can be obtained under local anaesthetic as a day procedure, and there should be little risk of any cosmetically unpleasant scar as the excision is done within the hairline over the temporal region. The specimens require careful pathological inspection so that short segments of inflammation are not missed.

Histopathologically, there are transmural inflammatory infiltrates most marked on the inner media adjacent to the internal elastic lamina, which typically is extensively disrupted in giant cell arteritis. The infiltrate is mononuclear but the giant cells that give the disease its name are only seen in approximately half of infiltrates examined. An infiltrate

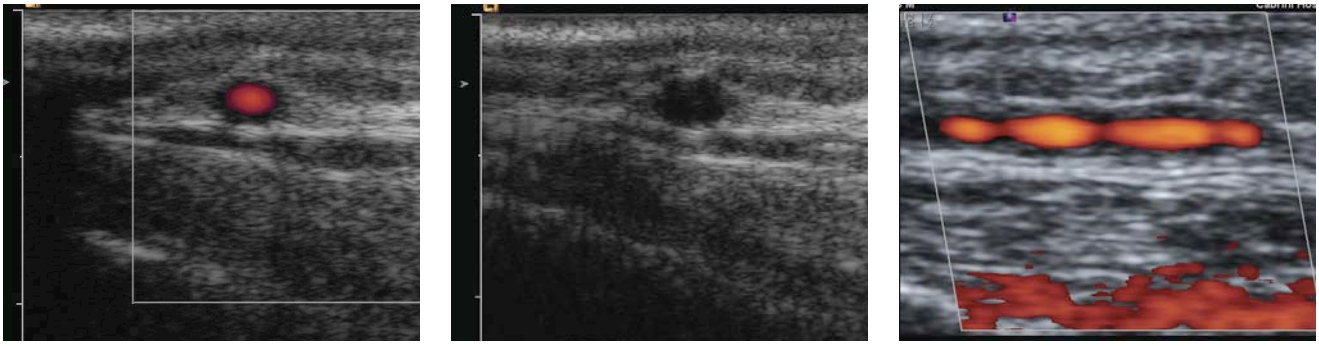

Figure 2. Giant cell arteritis – colour doppler ultrasounds. a (left). Transverse section of temporal artery showing dark, hypoechoic circumferential wall thickening ('halo') around the lumen of the artery with flow indicated by colour doppler. b (centre). Transverse section showing occlusion, as indicated by absence of colour signals. c (right). Longitudinal section showing multiple stenoses ('beading').

characterised by extensive polymorphonuclear cells raises the possibility of another form of systemic vasculitis affecting the temporal artery. Such an infiltrate has been reported in up to 10% of cases of systemic vasculitis.

Ultrasound of the temporal artery can further define the likelihood of giant cell arteritis. This examination can find stenoses or occlusions, with the most characteristic sign being a halo of oedema around the vessel media (Figures 2a to c). Some controversy surrounds the sensitivity of this procedure, although specificity of around 90% is generally accepted. Like all ultrasound procedures, the reliability of the procedure is dependent on the experience and expertise of the operator.

Positron emission tomography, an expensive investigation that is not readily available, has been found to be of value in assessing the activity of large vessel involvement, particularly of the aorta and its branches. It typically does not define involvement of the temporal artery, which is too small to visualise with this technique.

Management

Corticosteroid therapy remains the mainstay of treatment in giant cell arteritis. As well as protecting patients against visual loss, this therapy has dramatically improved their quality of life compared to the pre-corticosteroid era.

The dose of corticosteroid required to treat giant cell arteritis is higher than that required in polymyalgia rheumatica. However, there is no uniformity of opinion as to how much corticosteroid a patient with giant cell arteritis should receive. While it has been conventional to administer prednisolone in very high doses (50 to 100 mg) daily, there is no good data to support this policy. Giant cell arteritis can be well controlled in most patients with 25 mg prednisolone per day initially, although the dose may occasionally have to be increased for patients demonstrating treatment resistance and convention is to use higher doses in those cases with demonstrated visual loss. Studies of large numbers of patients with giant cell arteritis have convincingly shown that visual loss after the first month of corticosteroid therapy is very rare.

Corticosteroid dose reduction will allow the vast majority of patients to cease treatment by two years; patients continuing on prednisolone after this time will typically be taking doses of less than 5 mg daily. Withdrawing prednisolone within three months of initiation is not recommended, as this timeframe is not consistent with the natural history of the disease.

Methotrexate has been studied in several randomised controlled trials as an adjunctive agent in the treatment of giant cell arteritis, in an attempt to reduce prednisolone dosage. The results have been

mixed, but it would seem reasonable to use methotrexate (Ledertrexate, Methoblastin) in cases where corticosteroid reduction has proved difficult.

A strong case can be made for using low dose aspirin (Astrix, Cardiprin 100, Cartia) as an antithrombotic measure in the early phase of treatment of giant cell arteritis, when vascular occlusion is most likely to be a problem.

Complications of corticosteroid therapy

Corticosteroids are typically associated with the development of diabetes, hypertension, weight gain, thin skin with easy bruising, mood disturbance and osteoporosis. Careful monitoring for these complications is mandatory in the treatment of polymyalgia rheumatica and, particularly, giant cell arteritis, given the higher doses employed in that condition.

It is recommended that, at the very least, calcium and vitamin D supplementation be used to protect against corticosteroid-induced osteoporosis. Bisphosphonates, however, are generally seen as the treatment of choice in this situation, and every attempt should be made to determine whether patients are eligible for such therapy within PBS guidelines. It is possible that intravenous bisphosphonates such as zoledronic acid and disodium pamidronate may prove to be useful for protection against corticosteroid-related osteoporosis; however, final data concerning their effectiveness compared to oral bisphosphonates is not yet available.

If low dose aspirin is used in conjunction with corticosteroids, consideration should be given to prophylaxis against ulcer disease. Low dose aspirin is increasingly being recognised as a potent cause of ulcer disease, with up to 11% of patients taking it experiencing this complication. It is likely that more patients will be affected when corticosteroids are administered at the same time.

Conclusion

Both polymyalgia rheumatica and giant cell arteritis are common conditions of the elderly. Their management is fairly straightforward, once the diagnosis is established. The challenge lies in making the diagnosis with high certainty, and this requires a combination of clinical skills, diagnostic tests and careful follow up. MT

Further reading

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