A patient with bilateral shoulder and pelvic girdle aching

L H G Henskens general practitioner trainee, N Broos pharmacist, K Hautermans general practitioner

1Department of General Practice, Maastricht University, Maastricht, 6200 MD, Netherlands; 2Netherlands Pharmacovigilance Centre, Lareb's-Hertogenbosch, Netherlands

A 67 year old man, with a history of hypertension controlled with irbesartan with hydrochlorothiazide 300 and 12.5 mg/day, presented to his general practitioner with subacute onset of symmetrical aching and stiffness (most extreme in the morning) in his shoulders, pelvic girdle, and to a lesser extent his hands and knees, six days earlier. As a result, he had great difficulty turning over in bed, rising from a chair, and raising his arms above shoulder height. He also reported malaise and insomnia. He had no fever or other recent health problems. Twenty four hours before the onset of symptoms he had received the seasonal flu vaccine (Influvac 2009-10: A/Brisbane/59/2007, A/Brisbane/10/2007, B/Brisbane 60/2008).

Physical examination showed that he had difficulty raising his arms above shoulder height and rising from a chair. Both active and passive movements of the shoulders and hips were restricted because of muscle pain. Muscle weakness, erythema, and joint swelling were all absent. The temporal arteries seemed normal to palpation.

Biochemical investigations yielded an erythrocyte sedimentation rate of 7 mm in the first hour (reference range <20.0 mm), a C reactive protein concentration of 18 mg/L (<5), and a mild leucocytosis of 12.2×10⁹/L (4.0-10.0). Red blood cells, haemoglobin, thyroid hormones, aminotransferases, and creatinine kinase were all normal. Anticyclic citrullinated protein antibodies were absent.

We presumed a diagnosis of myalgia caused by viral infection or related to immunisation with flu vaccine and started him on a non-steroidal anti-inflammatory drug (diclofenac 100 mg twice daily). After three weeks, however, symptoms had not improved.

Questions

1 What is the most likely diagnosis?
2 What is the pathogenesis of this condition?
3 What differential diagnoses should be considered?
4 How would you treat this patient?
5 Are the patient’s symptoms or diagnosis linked to his recent immunisation with flu vaccine?

Answers

1 What is the most likely diagnosis?

Short answer

The clinical presentation—severe bilateral aching and stiffness of (sub)acute onset involving the shoulders and pelvic girdle in an elderly patient (>65 years), with no benefit of treatment with a non-steroidal anti-inflammatory drug—suggests a diagnosis of polymyalgia rheumatica.

Long answer

Polymyalgia rheumatica is the most common inflammatory rheumatic disease in older people. The incidence in UK primary care among people over 50 years is 8.4 per 10 000 person years. It is characterised by severe bilateral aching and stiffness of (sub)acute onset affecting the neck, shoulders, and pelvic girdle, and it is usually associated with a raised erythrocyte sedimentation rate or C reactive protein concentration, or both.

It has a great impact on quality of life. Patients are almost always over the age of 50 and usually over 65. Lack of uniform diagnostic criteria for polymyalgia rheumatica led to the establishment of international consensus classification criteria in 2008 (box 1). Although these criteria are awaiting prospective validation, they have been adopted by recently published guidelines for the management of this disease.

Polymyalgia rheumatica can be diagnosed in patients with normal inflammatory markers if there is a classic clinical picture and response to treatment. Our patient did not have a raised erythrocyte sedimentation rate, which is usually greater than 40 mm in the first hour in patients with this disease, although 7-22% of patients have an erythrocyte sedimentation rate below this value. These patients are characterised by younger age,
The causes of polymyalgia rheumatica are unknown. However, environmental and genetic factors are thought to contribute to disease susceptibility and severity.

Although the causes of polymyalgia rheumatica are unknown, both environmental and genetic factors are thought to contribute to disease susceptibility and severity. Marked geographical variations in the incidence of this disease, with higher rates at northern latitudes, implicate both environmental and genetic causes. An increased prevalence of antibodies against parainfluenza virus type 1 in patients and a close temporal relation between incidence peaks of polymyalgia rheumatica and epidemics of Mycoplasma pneumoniae, Chlamydia pneumoniae, and parvovirus B19 infections suggest an association between infection and the onset of disease. A proposed model for the pathogenesis of polymyalgia rheumatica involves both abnormal adaptive immune responses and an excessively activated innate immune system, which lead to subclinical vasculitis and a systemic inflammatory response, including synovitis in proximal joints and periarticular structures. Genetic variants of the HLA complex, which plays a central role in the immune response, seem to contribute to susceptibility to polymyalgia rheumatica and the severity of disease.

A patient reported global stiffness, night pain, and neurological signs, which are important differentials, their clinical features, and the necessary laboratory tests. Consider referral for specialist evaluation in patients younger than 60 years, those with chronic onset of symptoms (>2 months), lack of shoulder involvement, lack of inflammatory stiffness, “red flag” features (prominent systemic features, weight loss, night pain, and neurological signs), features of other rheumatic diseases, normal or extremely high acute phase response, uncertainty about the diagnosis, and treatment dilemmas (see answer to question 4). Urgent specialist referral is needed for suspected giant cell arteritis, which is seen in about 30% of people with polymyalgia rheumatica. Giant cell arteritis may lead to permanent partial or complete loss of vision in one or both eyes. Other severe vascular complications include stroke and, after several years, aortic aneurysm rupture.

Polymyalgia rheumatica usually responds rapidly to a moderate dose of prednisolone 15 mg daily, but long term treatment is needed. Guidelines recommend administration of prednisolone 15-20 mg daily. In patients without symptoms suspicious of giant cell arteritis, urgent steroid treatment is not indicated before clinical evaluation is complete. A patient reported global improvement of symptoms of 70% or more within one week of starting steroids, with normalisation of inflammatory markers in four weeks, is considered consistent with polymyalgia rheumatica. If the response to steroids is incomplete, poorly sustained, or completely lacking, higher doses of prednisolone should not be given before other conditions that present with similar symptoms have been excluded by specialist evaluation (table). However, patients with a typical clinical picture and complete sustained response to treatment without adverse events can be managed well in primary care. Importantly, long term treatment with steroids, with gradually tailored tapering and regular follow-up is required. Box 2 shows a suggested regimen for tapering of prednisolone, follow-up, and treatment of relapses. Non-steroidal anti-inflammatory drugs have little use in the management of this disease.

It can be difficult to diagnose polymyalgia rheumatica because of heterogeneity in clinical presentation, response to treatment, and disease course. The disease has a wide differential diagnosis including autoimmune, infectious, endocrine, and malignant disorders, which should be excluded by laboratory investigations before starting treatment. The table summarises the most important differentials, their clinical features, and the necessary laboratory tests.

<table>
<thead>
<tr>
<th>Box 1 International consensus classification criteria for polymyalgia rheumatica</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥50 years</td>
</tr>
<tr>
<td>• Bilateral shoulder or pelvic girdle aching, or both</td>
</tr>
<tr>
<td>• Duration ≥2 weeks</td>
</tr>
<tr>
<td>• Duration of morning stiffness &gt;45 minutes</td>
</tr>
<tr>
<td>• Evidence of an acute phase response (raised erythrocyte sedimentation rate or C reactive protein, or both)*</td>
</tr>
<tr>
<td>• Rapid response to treatment (&gt;70% within one week)</td>
</tr>
</tbody>
</table>

*Polymyalgia rheumatica can be diagnosed when inflammatory markers are normal, if there is a classic clinical picture and the patient responds to treatment.
in this phenomenon, but this does not mean that flu vaccination is the cause of polymyalgia rheumatica in our patient.

**Long answer**

An association between flu vaccination and polymyalgia rheumatica has been described in a small number of case reports.\(^1\)\(^\text{11-13}\) Since 2006, six other cases of polymyalgia rheumatica after immunisation with flu vaccine have been reported to the Netherlands Pharmacovigilance Centre Lareb (www.lareb.nl; English version available; consulted May 2011). Polymyalgia rheumatica is an immune mediated disease involving environmental and genetic factors.\(^1\)\(^\text{11-13}\) Vaccines may trigger autoimmune diseases, particularly in genetically predisposed people.\(^1\)\(^\text{15-20}\) Genetic studies have implicated genes of the HLA complex in the aetiology of this disease.\(^1\)\(^\text{11-13}\) In particular, genetic variants of HLA-DRB1 seem to contribute to disease susceptibility and severity.\(^1\)\(^\text{11-13}\) HLA-DRB1 is a major histocompatibility complex class II cell surface receptor on antigen presenting cells that plays a central role in the immune response by presenting peptide antigens derived from extracellular proteins to T cells.\(^1\) Polymyalgia rheumatica has been linked to certain HLA-DRB1 alleles—HLA-DRB1*04, HLA-DRB1*01, HLA-DRB1*13, and HLA-DRB1*14.\(^1\)\(^\text{11-13}\) Typing of HLA-DRB1 alleles in our patient showed the presence of HLA-DRB1*14:54. It is possible that the flu vaccine antigen induced an autoimmune reaction in the presence of the HLA-DRB1*14:54 allele, which clinically manifested as polymyalgia rheumatica. The close temporal association between vaccination and onset of symptoms—within 24 hours—supports a causal relation between the vaccine and polymyalgia rheumatica, although it also possible that the disease was not caused by the vaccine. In the assessment of vaccine safety, it is important to consider background rates of disease.\(^27\) Using Dutch incidence rates of polymyalgia rheumatica (9/10 000 person years)\(^*\) it can be calculated that during a flu vaccine campaign in the Netherlands, during which five million people could be vaccinated over a period of three months, 1125 new cases of PMR would be predicted to occur as background coincident cases.

Whether this patient should not be immunised again to avoid future cases?

**Patient outcome**

On the basis of the clinical presentation, we presumed a diagnosis of polymyalgia rheumatica and administered prednisolone 15 mg daily, in line with current guidelines.\(^3\)\(^\text{6}\) However, symptoms did not respond to treatment after 10 days. Therefore, prednisolone was withdrawn and the patient was referred for specialist evaluation. Laboratory investigations yielded an increasing erythrocyte sedimentation rate of 25 mm in the first hour, a steady C reactive protein concentration (48 mg/L), and persisting leucocytosis (12.4×10\(^\text{9}\) \text{L}\(^\text{-}\)\text{1}\)). Antinuclear antibody concentrations and total serum protein values were normal. Paraproteins were absent. Chest radiography and ultrasound imaging of the abdomen showed no abnormalities. Bone scintigraphy showed enhanced activity in both shoulders indicating osteoarthritis. By exclusion of other conditions, a diagnosis of polymyalgia rheumatica was again made.

Prednisolone 30 mg daily was given and the patient reported a rapid relief of his symptoms within a few days. Two weeks later his erythrocyte sedimentation rate had decreased to 4 mm in the first hour, C reactive protein had dropped to 3 mg/L, and leucocytosis had also normalised. After six months of treatment prednisolone was gradually tapered to 5 mg daily. Lower doses, however, led to recurrence of symptoms.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/doi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

---

**Box 2 Suggested regimen for tapering of prednisolone and treatment of relapses\(^4\)\(^\text{6}\)**

**Tapering of prednisolone**

- Week 0-4: 15 mg daily (with a visit to the doctor at weeks 1 and 4)
- Week 5-8: 12.5 mg daily (with a visit to the doctor at week 8)
- Week 9-12: 10 mg daily (with a visit to the doctor at week 12)
- Week 13 onwards: reduce by 1 mg every 4-8 weeks according to symptoms and erythrocyte sedimentation rate or C reactive protein values, or both; follow up at 6, 9, and 12 months, with extra visits for relapses and adverse events

**Relapses**

- In patients with one or two relapses increase prednisolone to the previously effective dose; try to taper the dose after four weeks according to symptoms and erythrocyte sedimentation rate or C reactive protein value, or both.
- In patients with three or more relapses increase prednisolone to 1-2 mg above the previously effective dose with slow tapering by 1 mg every one to three months.

\*Defined as recurrence of symptoms or increase in erythrocyte sedimentation rate or C reactive protein value, or both.

---


---

For personal use only: See rights and reprints [http://www.bmj.com/permissions](http://www.bmj.com/permissions) Subscribe: [http://www.bmj.com/subscribe](http://www.bmj.com/subscribe)

Cite this as: BMJ 2011;343:d6233
© BMJ Publishing Group Ltd 2011
**Table**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical features</th>
<th>Laboratory investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Predominant peripheral joint symptoms</td>
<td>Rheumatoid factor, anticyclic citrullinated protein antibodies, radiography</td>
</tr>
<tr>
<td>Late onset spondyloarthropathy*</td>
<td>Predominant low back stiffness and pain</td>
<td>Radiography</td>
</tr>
<tr>
<td>RS3PE syndrome†</td>
<td>Peripheral hand or foot oedema</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus, scleroderma, Sjögren’s syndrome, vasculitis</td>
<td>Fatigue, stiffness, multisystem disease</td>
<td>Antinuclear and antineutrophil cytoplasmic antibodies</td>
</tr>
<tr>
<td>Dermatomyositis, polymyositis</td>
<td>Proximal muscle weakness</td>
<td>Creatine kinase**</td>
</tr>
<tr>
<td><strong>Non-inflammatory disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis, spinal spondylosis</td>
<td>Articular pain of shoulder, neck, and pelvic girdle</td>
<td>Radiography</td>
</tr>
<tr>
<td>Rotator cuff disease, adhesive capsulitis</td>
<td>Capsular restriction, periarticular pain</td>
<td>Ultrasonography (magnetic resonance imaging)</td>
</tr>
<tr>
<td>Infections‡</td>
<td>Fever, weight loss, deep soft tissue, and bone pain</td>
<td>Full blood count**, erythrocyte sedimentation rate**, C-reactive protein**, urinalysis**</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Stiffness, rigidity, shuffling, staring, gradual onset</td>
<td></td>
</tr>
<tr>
<td>Chronic pain syndrome, fibromyalgia, depression</td>
<td>Tender points, fatigue, longstanding history</td>
<td></td>
</tr>
<tr>
<td>Endocrinopathy and metabolic bone disease¶</td>
<td>Bone pain, fatigue</td>
<td>Thyroid stimulating hormone**, parathyroid hormone, calcium**, phosphorus, vitamin D concentration</td>
</tr>
</tbody>
</table>

*Including ankylosing spondylitis, psoriatic arthritis.
†RS3PE=rermitting seronegative symmetric synovitis with pitting oedema.
‡Including viral syndromes, osteomyelitis, bacterial endocarditis, tuberculosis.
§Including lymphoma, leukaemia, myeloma, amyloidosis, occult solid tumours.
¶Including hyperthyroidism, hypothyroidism, hyperparathyroidism, hypoparathyroidism, hypovitaminosis D, osteomalacia, pseudogout with calcium pyrophosphate deposition.
**Basic biochemical investigations obligatory before starting treatment.

---

BMJ: first published as 10.1136/bmj.d6233 on 14 October 2011. Downloaded from http://www.bmj.com on 26 July 2022 by guest. Protected by copyright.