CASE REPORT

Diffuse idiopathic skeletal hyperostosis and isotretinoin in cystic acne

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SUMMARY

We present the case of a 35-year-old man with thoracic back pain and stiffness, whose only medical history was cystic acne treated with repeated courses of retinoids. His thoracic spine was severely limited in range of movement and was found, on X-ray, to have unilateral hyperostosis typical of diffuse idiopathic skeletal hyperostosis (DISH)—an often asymptomatic condition rarely found in those under 50. Back stiffness in young patients with prolonged retinoid exposure should be investigated.

BACKGROUND

Diffuse idiopathic skeletal hyperostosis (DISH) is a prevalent but mostly asymptomatic condition of the elderly, often not distinguished from osteoarthritis. It is poorly understood and its management is symptomatic. Reports have associated it with prolonged use of retinoids, however, this is not widely known. Use of retinoids for acne in the young has been increasing. Although back pain is common and should not be over investigated, this case raises awareness of the association between prolonged retinoid therapy and DISH. Thoracic pain, stiffness and enthesal symptoms in such patients warrant imaging and cessation of retinoids if DISH is found.

CASE PRESENTATION

A 35-year-old previously well man was referred to rheumatology with a 1-year history of thoracic back pain. He was previously fit and a keen cyclist. His only medical history was cystic acne since the age of 15, requiring repeated courses of isotretinoin. He received four courses (each at the standard 500 µg/kg/day oral dose for 6 months) and a final long-term course gradually down-titrated to 20 mg/day. This course was, however, stopped after a year due to adverse effects on his mood, which was approximately a year before onset of back pain.

His thoracic back pain was severe and sharp in nature. The pain was exacerbated by activity and radiated to the lower back. Early morning stiffness lasted up to an hour. There were no symptoms localising to cervical or lumbar spine, or sacroiliac joints. He also reported occasional pain at the Achilles' tendon insertion, but no other peripheral joint or enthesal symptoms.

The patient has never smoked and consumed alcohol socially. The only family history was of age-appropriate osteoarthritis.

On examination, his blood pressure was 136/85. There were facial scars from previous acne. His thoracic spine was stiff allowing virtually no forward flexion, extension or lateral flexion.

Circumferential chest expansion was reduced at 4 cm (5th centile for his age). Cervical and lumbar spine had full range of movement in all planes. There was no sacroiliac tenderness on palpation or stressing. Examination of peripheral joints and other systems was unremarkable.

INVESTIGATIONS

Routine blood results were normal, including bone profile (alkaline phosphatase 56 u/L, parathyroid hormone 4.7 pmol/L) and vitamin D (54 nmol/L). Vitamin A level was normal at 2.5 µmol/L. Metabolic screen revealed normal fasting glucose (5.8 mmol/L), B₁₂ and folate. Fasting lipids were mildly deranged (normal range in parentheses): cholesterol 5.1 mmol/L (<5 mmol/L), triglycerides 1.9 mmol/L (<1.7 mmol/L), high-density lipoprotein 0.8 mmol/L (>1.2 mmol/L) and low-density lipoprotein 3.4 mmol/L (<3 mmol/L). Serum urate was elevated (526 µmol/L). Inflammatory markers including erythrocyte sedimentation rate (2 mm/1 h) and C reactive protein (1 mg/L) were within the normal reference range. Human leucocyte antigen-B27 was negative.

Anteroposterior radiographs of the thoracic spine revealed typical right-sided hyperostosis (figure 1). MRI of the whole spine showed no perilesional inflammatory changes or nerve compromise. Sacroiliac joints were normal.

DIFFERENTIAL DIAGNOSIS

Young males presenting with chronic back pain and stiffness should also be considered for inflammatory axial spondyloarthritis, such as ankylosing spondylitis. Hyperostosis and acne are also part of SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis).

TREATMENT

The patient initially reported minor symptomatic improvement with non-steroidal anti-inflammatory drugs (NSAIDs), however, pain and stiffness continued to be problematic. Currently, he has stopped NSAIDs and is experiencing some relief from gabapentin. General physiotherapy was not reported to be beneficial and he is awaiting hydrotherapy.

DISCUSSION

DISH is characterised by enthesal ossification. Involvement of the anterolateral aspect of the thoracic spine is typical, although peripheral entheses can also feature, as in this case.¹

Prevalence of DISH is reported to be up to 28% but is very rare in those under 40 years of age.² It is

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Figure 1 Anteroposterior and lateral radiographs of thoracic spine showing right-sided 'flowing' calcifications.

an asymptomatic condition in many individuals, and can be difficult to distinguish from osteoarthritic changes in the elderly, in whom it is much more common. The radiological appearances are typically right-sided and distinct from the vertebral bodies. The diagnostic criteria by Resnick and Niwayama³ are:

- ▶ 'flowing' Calcification and ossification along the anterolateral aspects of at least four contiguous vertebral bodies,
- ▶ Preservation of disc height in the involved areas and the absence of radiographic changes of 'degenerative' disc disease,
- ▶ Absence of apophyseal joint bony ankylosis and sacroiliac joint disease.

Given this patient's advanced hyperostosis at an unusually young age and cumulative dose exposure, it is felt that isotretinoin is associated with DISH in this case. However, his risk factors for this painful presentation are unknown.

The pathogenesis of DISH is unclear. It is associated with metabolic disturbances such as hypertension, hyperglycaemia/hyperinsulinaemia, dyslipidaemia and hyperuricaemia, which should be screened for and managed, in order to reduce cardiovascular risk.⁴ This patient fulfilled the National Cholesterol Education Programme ATP III criteria for metabolic syndrome (for hypertension and dyslipidaemia).⁵

Insulin promotes mesenchymal cell differentiation and enchondral ossification.⁶ Therefore, hyperinsulinaemia may have a role in pathophysiology of DISH. It is also possible that low grade inflammation associated with these metabolic disturbances may contribute to the development of ossification. However, in a small case-control study, insulin, lipids and uric acid were not different between the matched groups.⁷

Retinoic acid is essential for mesenchymal cell differentiation and embryonic skeletal development as well as for influencing

normal bone metabolism.⁸ Cortical thickening or periosteal reactions of long bones in children have been reported in children after long-term ingestion of large amounts of vitamin A (retinol) supplements.

Isotretinoin is a synthetic retinoid used to treat cystic acne. Its association with hyperostosis has been reported since 1983 in several case series⁸ and in postmarketing information by its producer.⁹ In a study of 96 patients treated for cystic acne with isotretinoin, 26% were found to have new vertebral spurs by 2-year follow-up, although there was no control group.¹⁰ The average age was 25 years and most received only one course of 4–5 months' treatment.

It is possible that use of synthetic retinoids may cause mesenchymal stem cell proliferation and differentiation to form osteoblasts in the entheses leading to ossification. However, the causal link is unclear; serum retinol and retinoid binding protein was not different in DISH cases compared with matched controls.⁷ It is important to note that isotretinoin is also reported to cause dyslipidaemia, hyperuricaemia and, possibly, disruption of glucose metabolism,⁹ although it is not known whether these metabolic disturbances continue after withdrawal of therapy.

Treatment of DISH is largely symptomatic with analgesia and physiotherapy much as in osteoarthritis. Hyperostosis may rarely lead to nerve and oesophageal compression that require surgical input.¹¹ It is unclear why pain featured prominently in this case while many cases of DISH are asymptomatic. There was no appreciable inflammation or nerve involvement; however, this condition still has many unknown factors, as is the case with any painful disorder. There may also be reporting bias in younger compared to older patients in whom back pain of all aetiologies is more prevalent.

NSAID administration has been highlighted as a potential preventative intervention for heterotopic ossification in DISH,⁴ although, to date, there are no clinical trial data to support its

Patient's perspective

- ▶ This life changing condition has affected me physically, emotionally and mentally. Once an extremely active individual, I can no longer carry out my sporting hobbies through lack of movement and severe pain.
- ▶ General everyday tasks I once took for granted have become a burden through pain and I have had to end active employment because of this. My sleeping pattern is severely disrupted through pain, stiffness and discomfort. I have been prescribed numerous NSAIDs, none of which have been successful. I have tried physiotherapy to improve my lack of movement, with zero improvement.
- ▶ I am extremely upset by the lack of knowledge, treatment and understanding of DISH and its link with Isotretinoin. I would have reconsidered agreeing to use this drug if I knew all of the risks with long-term treatment.

Learning points

- ▶ Diffuse idiopathic skeletal hyperostosis (DISH) is a prevalent but mostly asymptomatic condition of the elderly.
- ▶ DISH may be associated with prolonged retinoid therapy.
- ▶ Thoracic pain, stiffness and enthesal symptoms in such patients warrant imaging and cessation of retinoids if DISH is found.

disease modifying role. Heterotopic ossification is thought to occur at sites of inflammation. NSAIDs target inflammation via cyclooxygenase inhibition, thus limiting expression of prostaglandin E2 and other chemokines.

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