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CASE REPORT
ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

Ankylosing spondylitis manifested as unexplained leukocytosis

Ankylosing spondylitis is a potentially disabling inflammatory arthritis of the spine, usually presenting as chronic back pain, typically before the age of 45 years. The case is presented of a nurse aged 32 years who developed the condition. The special interest and rarity of this case is the fact that unexplained leukocytosis was present for at least ten years before the appearance of arthritis and diagnosis of the disease.

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2021, 38(5):664–666

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Αγκυλοποιητική σπονδυλίτιδα με πρώτη εκδήλωση ανεξήγητη λευκοκυττάρωση

Περίληψη στο τέλος του άρθρου

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Ankylosing spondylitis (AS) is the prototype of the immune-mediated inflammatory rheumatic diseases grouped under the term spondyloarthritis. Early diagnosis has become increasingly important, because effective treatment is available, and anti-tumor necrosis factor (anti-TNF) drugs are more effective when administered in the early stages of the disease.[1] The case is presented here of AS initially manifested as unexplained leukocytosis of least 10 years' duration.

CASE PRESENTATION

A 32-year-old woman, attended the outpatient department of Troodos hospital for investigation of unexplained leukocytosis of at least 10 years' duration. She also reported occasional pain in the distal metacarpophalangeal joints. Her medical history included a miscarriage at the eighth week of pregnancy 10 years previously, as a result of thrombosis of the placenta, at which time leukocytosis was detected. She had two subsequent full-term pregnancies, during which she took aspirin and low molecular weight heparin. She reported an episode of uveitis three years ago during her second pregnancy. In addition, she reported a laparoscopic cholecystectomy, laparoscopic removal of a serous cystadenoma of the right ovary and pityriasis rosea. She works as a nurse and has a 6 pack-years history of cigarette smoking. Her family history included type 2 diabetes mellitus (DM), arterial hypertension, psoriasis and dyslipidemia (father) and hypothyroidism (mother).

On examination the patient was afebrile and hemodynamically stable (blood pressure 120/89 mmHg, pulse rate 90/min). Her systems examination was normal and there were no signs of arthritis.

Laboratory investigation showed: White blood cell count (WBC) 12,990 μL (neutrophils 59.1%, lymphocytes 32.9%, monocytes 5%), hematocrit (Hct) 44.9%, Hb 14.9 g/dL, platelets (Plt) 455×10^3/μL, fibrinogen 535.3 mg/dL, erythrocyte sedimentation

rate (ESR) 12 mm/h and C-reactive protein (CRP) 13 mg/L. Microscopic examination of peripheral blood revealed large platelets, microcytosis with mild toxic granulation of neutrophils and some reactive lymphocytes. Biochemical examination was normal and urinalysis revealed asymptomatic bacteriuria. Serum protein electrophoresis and full immunological tests were normal with the exception of lupus anticoagulant (LA) which was positive. A complete molecular test for thrombophilia and *CALR+JAK2* genes was negative. Two pairs of blood cultures were negative. Serological tests for human immunodeficiency virus (HIV), and hepatitis C virus (HCV) were negative, and for hepatitis B (HBV) tests revealed past immunization.

Reassessment four months later showed no change in the clinical picture. Laboratory tests again revealed leukocytosis, WBC 12,580/μL, and Plt 521×10^3μL, ESR 17 mm/h, CRP 4 mg/L, and fibrinogen 560 mg/dL. Microscopic examination of the peripheral blood showed some large platelets, anisocytosis and few reactive lymphocytes. LA was negative.

Two months later the patient reported tiredness and progressively worsening pain in the left hip, lumbar spine, sacroiliac joints and right shoulder. She had also morning stiffness which lasted for about two hours and ankle pain in the morning. Her symptoms were relieved on moving. She also complained of occasional episodes of diarrhoea. On examination she showed signs of right rotator cuff tendinopathy, tenderness in the thoracic and lumbar spine and in both sacroiliac joints, more on the left. Her Schobers test was +4 cm, wall to tragus distance was 13 cm and chest expansion was +3 cm. Her Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was 9. Magnetic resonance imaging (MRI) of the lumbar spine showed circular disk bulging annulus fibrosus of L3–L4, with mild pressure on the spinal nerve roots, and foraminal disc herniation of L4–L5. MRI of the sacroiliac joints showed minor sclerosing findings and erosions of subchondrial bone anterior-inferior to the sacroiliac joints bilaterally. These findings were compatible with chronic sacroiliitis of both sacroiliac joints. The diagnosis of AS with peripheral involvement was made.[1] She was started on regular Naproxen 500 mg twice daily, and physiotherapy for stretching exercises. As her BASDAI score remained high despite regular nonsteroidal anti-inflammatory drug treatment (NSAIDs) (BASDAI score 7.8), she was started on regular anti-TNF therapy. On review after five months of treatment, she reported improvement in her symptoms (BASDAI score 4), including her diarrhoea.

DISCUSSION

AS is a chronic inflammatory rheumatic disease characterized by inflammation of the soft tissues surrounding the spine and pelvis. AS pathogenesis has not yet been fully elucidated, although there is a familial association with human leukocyte antigen HLA-B27 expression.[2] The disease is typified by upregulation of proinflammatory cytokines, including such as TNF-α, interleukin-1 (IL-1), and IL-23/IL-17.[3] Commonly the level of CRP is high, but only weak correlation is noted between WBC and CRP.[4] There are indications that the peripheral blood of patients with AS contains activated immune cells, and the percentages of Th17 and Th1 cells in peripheral blood mononuclear cells are significantly increased in patients with AS. The levels of cytokines and specifically IL-8, are also raised.[5] The nucleotide-binding oligomerization domain (NOD) appears to be involved. The pro-inflammatory cytokines, IL-1β and IL-18, activate the NACHT, leucine-rich repeat (LRR) and PYD domain-containing protein-3 (NLRP3) inflammasome.[6] There appears to be an association of the NLRP3 inflammasome with AS pathogenesis.[6] This inflammasome is stimulated by Toll-like receptors, or NOD-like receptors, by a diverse array of "danger signals" such as pathogenic microbes, bacterial DNA, lipopolysaccharides (LPS), uric acid, silica, and alum.[7]

The case described here is unusual in that leukocytosis preceded the clinical manifestation of AS by several (at least 10) years. A case of Crohn's disease with spondylitis of the pelvis, presenting with leukocytosis was described almost 50 years ago.[8] A case of AS with an inflammatory granuloma like tissue and neutropenia has also been described.[9] Such cases hint that an inflammatory response, possibly to microbes, precedes the inflammasome activation that leads to activation of T-lymphocytes in AS.[5,10]

The observation that leukocytosis can precede the AS, may shed light on the role of inflammasome activation of auto-immune processes that eventually involve the spinal soft tissues. The connection might be the enigmatic IL-6, which has context-dependent pro- and anti-inflammatory roles.[11]

Leukocytosis is quite common in established AS, occurring in about 20% of patients, but it is often dismissed as a minor part of the auto-immune process.[3] In this case the leukocytosis preceded the development of the auto-immune process, which indicates that the leukocytosis might be the primary inciting event.[12] Progress in genetics and the findings of autoantibodies in AS spondylitis raise again the question of autoimmune vs autoinflammatory etiology. Recent attention has been focused on the roles of microbiota and biomechanical stress in initiating and perpetuating inflammation that eventually leads to the auto-immune damage. There are indications that LPS are potent activators of the inflammasomes, and in addition to augmenting NLRP3 inflammasome activity via NLRP3 induction, LPS boosts caspase-1 activation by the NLRP3 and AIM2 inflammasomes by an acute mechanism that is independent of inflammasome sensor induction.[13] It is hypothesized that LPS exposure might activate the inflammatory process that eventually culminates in spondyloarthropathy.

ΠΕΡΙΛΗΨΗ

Αγκυλοποιητική σπονδυλίτιδα με πρώτη εκδήλωση ανεξήγητη λευκοκυττάρωση

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Η αγκυλοποιητική σπονδυλίτιδα είναι μια δυνητικά καταστρεπτική μορφή φλεγμονώδους αρθρίτιδας που εμφανίζεται συνήθως με χρόνιο άλγος στην οσφύ, κυρίως πριν από την ηλικία των 45 ετών. Ένα τέτοιο περιστατικό της νόσου, σε μια νοσηλεύτρια 32 ετών, περιγράφεται στην παρούσα εργασία. Το ιδιαίτερο ενδιαφέρον και η σπανιότητα της περιγραφείσας περίπτωσης αφορά στο γεγονός ότι της πλήρους εκδήλωσης της νόσου προηγήθηκε ανεξήγητη λευκοκυττάρωση για χρονικό διάστημα τουλάχιστον 10 ετών.

Λέξεις ευρετηρίου: Αγκυλοποιητική σπονδυλίτιδα, Λευκοκυττάρωση, Φλεγμονόσωμα

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