

Seronegative polyarthritis as severe systemic disease

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ABSTRACT

Background: Severe extra-articular disease is associated with high levels of rheumatoid factor (RF) in patients with seropositive rheumatoid arthritis (RA) and a poor prognosis. It is said that patients with seronegative rheumatoid arthritis have a more benign course and less destructive disease. We observed several patients with seronegative non-rheumatoid polyarthritis, with aggressive extra-articular systemic disease.

Objectives: Review of seronegative systemic polyarthritis with clinical presentation of typical cases.

Methods: Medline search for systemic manifestations of seronegative polyarthritis. **Clinical presentations:** 1. A 56-year-old woman was admitted to the cardiac intensive care unit with stabbing presternal chest pain aggravated by breathing and progressive dyspnoea, which gradually developed over a period of two weeks with one episode of fever at 38.0 °C. She had suffered chronic pain in her buttocks for three years with polyarthralgia and evanescent palmar-plantar rash. Imaging showed bilateral sacroiliitis (HLA B27 negative) and a large pericardial effusion. Extra-articular manifestations of SAPHO syndrome were proposed and she was successfully treated with combined therapy: pulse methylprednisolone, azathioprine, colchicine and prednisone. 2. A 47-year-old woman with psoriatic arthropathy developed high fever with leucocytosis and thrombocytosis and lung infiltrates during exacerbation of her joint disease. She was treated with pulse methylprednisolone followed by corticosteroid tapering, anti-TNF (infliximab) and methotrexate with complete resolution. 3. A 19-year-old man with inflammatory bowel disease developed acute pericarditis with response to 6-mercaptopurine, salazopyrine and prednisone.

Results: We discuss a range of seronegative arthritis diseases with possible systemic manifestations including the main procedures for early diagnosis. Infection,

malignancy, hypersensitivity, granulomatous disease and other collagen diseases such as systemic lupus erythematosus should be excluded, but investigations for an underlying disease should not delay early corticosteroid and immunosuppressive therapy.

Conclusion: A high level of suspicion of extra-articular disease should always be maintained when treating active seronegative polyarthritis.

KEYWORDS

Seronegative polyarthritis, sacroiliitis, pleuro-pericarditis, pneumonitis, SAPHO syndrome

RHEUMATOID FACTOR AND ITS BIOLOGICAL ROLE

Rheumatoid factor (RF), as a marker of seropositive rheumatoid arthritis, is an autoantibody (usually IgM) against the Fc portion of IgG. By forming immune complexes, RF initiates the universal mechanism of immunoglobulin elimination by the reticuloendothelial system. That is why RF is present in small titres in all people, being in higher titres (above 20 IU/ml) in less than 5% of the population. The incidence of high titres of rheumatoid factor increases with age and more than 20% of people over the age of 65 years have an elevated rheumatoid factor. High levels of RF are associated with severe destructive joint disease, extra-articular involvement (lung, vasculitis, subcutaneous nodules) and poor prognosis. As a much more specific addition to RF detection, anti-cyclic citrullinated peptide antibodies (anti-CCP) has recently become an important diagnostic tool for confirming RA seropositivity.

SERONEGATIVITY

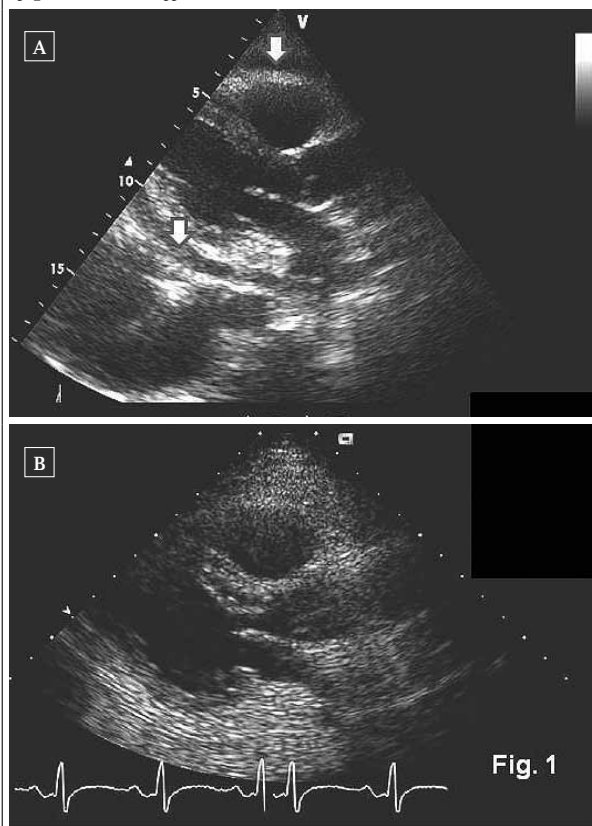
Patients who do not have detectable RF are said to be 'seronegative' (SNA). Patients with seronegative rheumatoid arthritis are thought to have a more benign course and less destructive disease. Spondyloarthropathies are diseases not associated with increased RF. In this article seronegative polyarthritis is considered to be not only spondyloarthropathy disease but all arthritides with negative IgM RF. We observed several patients with seronegative non-rheumatoid polyarthritis (SNA), with aggressive extra-articular systemic disease, requiring prompt diagnostic and therapeutic decisions.

CLINICAL PRESENTATIONS OF SERONEGATIVE SYSTEMIC POLYARTHRITIS

Case 1

Our first case concerns a 56-year-old woman who was admitted to the cardiac intensive care unit with stabbing presternal chest pain aggravated by breathing and progressive dyspnoea. Her symptoms developed gradually over a period of two weeks with one episode of fever at 38.0 °C. Her preceding disease comprised chronic pain in the buttocks for three years with polyarthralgia and evanescent palmar-plantar rash. The pain in the buttocks had increased before admission. Her other medical problems were acute gastroenteritis one month ago, subacute thyroiditis one year ago with further normal thyroid function, achalasia with severe oesophageal distension for 30 years, pleural effusion of unknown origin nine years ago and hypersensitivity to penicillin. She had not received any medications before admission. Vital signs on admission were as follows: blood pressure 120/90 mmHg, pulse 110 beats/min, temperature 37.0 °C, respiratory rate 32/min. Physical examination revealed congested neck veins, left subscapular dullness, decreased respiratory sounds, muffled cardiac sounds, no abdominal organ enlargement, and tenderness above the sacroiliac joints. Chest X-Ray showed cardiomegaly and bilateral pleural effusion. CT angiogram of the chest excluded pulmonary embolism and showed large pericardial effusion, bilateral small pleural effusion, multiple lung infiltrates, and achalasia. ECG demonstrated low voltage. Pelvis CT displayed stage II bilateral sacroiliitis. Echocardiography confirmed large pericardial effusion with fibrin deposits (*figure 1A*), preserved ventricular function and no valve disease. Laboratory investigation showed microcytic anaemia (haemoglobin 10.1 g/dl), leucocytosis 16,900 per μ l (polymorphonuclear neutrophils (PMN) 78%), thrombocytosis 6×10^5 per μ l, albumin 2.5 g/dl, normal

Figure 1. A. Echocardiography on admission (parasternal long axis) demonstrating pericardial effusion (arrows). B. Echocardiography two months after admission (parasternal view) demonstrating resolution of pericardial effusion



troponin, erythrocyte sedimentation rate (ESR) 50 mm/h, C-reactive protein 21.1 mg/dl ($n < 0.5$), mildly elevated alkaline phosphatase and borderline increased ferritin, normal renal function, and no proteinuria. Blood and urinary cultures were negative. Pericardiocentesis yielded 0.5 litre of serosanguinous exudate containing 72% PMN and 28% mononuclear cells, a high lactate dehydrogenase concentration (620 IU/l) and normal glucose level. Gram staining, culture, pericardial fluid cytology and Ziehl-Neelsen staining were all negative. Blood and pericardial fluid virology tests, also including EBV, Coxsackie viruses and hepatitis, were negative. The diagnosis of polyserositis and pneumonitis in the presence of sterile blood and pericardial exudate and high level of acute phase response (ESR, CRP, low albumin) led us to a possible autoimmune disease, probably related to sacroiliitis and palmar-plantar rash (SAPHO syndrome). The low level of ferritin did not support the diagnosis of Still's disease. Hypersensitivity was unlikely because of the lack of an offending drug and exposure. Malignancy had not been found. Immunological profile: RF, anti-CCP, ANA, antibodies to extractable nuclear antigens (SSA, SSB, SM, RNP), ANCA, anticardiolipin antibodies, and

cryoglobulins were all negative. Protein electrophoresis revealed polyclonal hypergammaglobulinaemia. Systemic lupus erythematosus and collagen vascular disease, despite negative immunological tests, were doubtful. Methylprednisolone intravenous pulses of 500 mg per day for three days with further prednisone therapy (1 mg/kg) brought about a rapid improvement. The white blood count (WBC) count increased to 40,000 per μ l after corticosteroid (CS) administration and decreased to 10,600 per μ l after starting azathioprine (AZA) therapy as steroid sparing agent. AZA was considered after relapse of the chest pain after CS tapering to a dose below 20 mg/day. Pleural and pericardial effusion were completely resolved (figure 1B).

Case 2

Our second case concerns a 47-year-old woman with a two-year history of psoriatic arthropathy and fever of 39.5 °C, asymmetric joint and spine pain, finger swelling and stiffness on admission without respiratory complaints. The chest CT revealed two small infiltrates in lower lobe of the left lung and one small basal right lower lobe infiltrate with mediastinal lymphadenopathy (figure 2). Cell blood count showed leucocytosis (13,000) and thrombocytosis (7×10^6). Tuberculosis, bacterial and viral pneumonia, granulomatous disease and malignancy were excluded, trial of antibiotic therapy failed and the patient responded to methylprednisolone therapy. Further activity of inflammatory disease was suppressed by CS, methotrexate and anti-TNF (infliximab) therapy with complete resolution of lung abnormalities, active polyarthrititis and fever.

Case 3

A 19-year-old man was admitted with abdominal pain and bloody diarrhoea and chest pain, aggravated by deep breathing. Abdominal CT and colonoscopy revealed ulcerative colitis and sacroiliitis and chest CT showed

moderate pericardial effusion. The patient responded to intravenous corticosteroid pulse therapy, and combined therapy including 6-mercaptopurine, salazopyrine, and prednisone with complete resolution of active colitis and pericardial effusion. Chest pain and pericardial effusion was an unusual systemic presentation of ulcerative colitis!

DIAGNOSTIC ALGORITHM FOR SERONEGATIVE SYSTEMIC POLYARTHRITIS

We discuss a range of seronegative arthritis diseases including the main procedures for early diagnosis (figure 3).

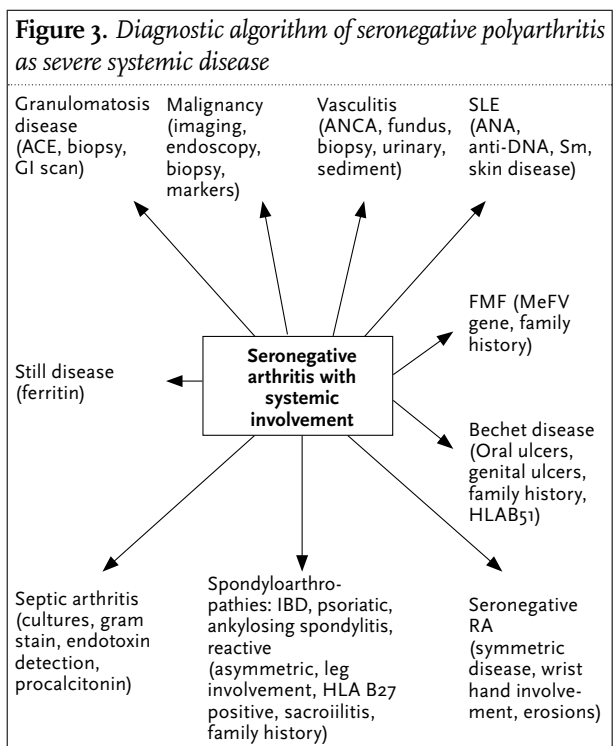
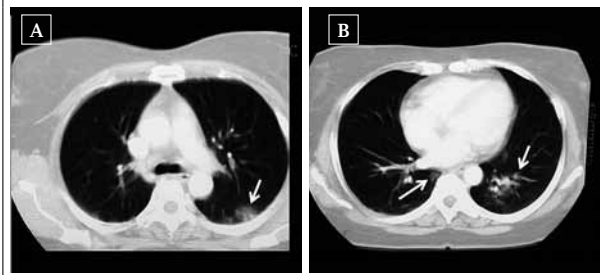


Figure 2. A. CT scan of the chest at the level of carina, lung window. Small patchy ground glass subpleural opacity in the apical segment of the left lower lobe is seen. B. CT scan of the chest at the level of right inferior pulmonary vein, lung window. Vague ground glass opacity around pulmonary vessels of the left lower lobe and small patchy opacity in the right lower lobe are seen.



PREDICTORS OF SYSTEMIC MANIFESTATIONS

In the multivariate analysis, extra-articular RA (ExRA) manifestations were predicted by the presence of a positive RF (RR 1.56), ANA test (RR 1.58), smoking (RR 1.52) and severe disability (Steinbrocker Class III-IV at diagnosis) (RR 1.42) but not by age and sex.¹ In a subgroup of 12.8% with severe ExRA (Malmo criteria) the main predictors were smoking (RR 2.94), early disability (RR 2.45). RF was weakly associated with ExRA Malmo (severe extra-articular disease) compared with seronegative RA, but smoking, early disability and old age were stronger predictors than

RF for severe ExRA.¹ Such data estimating extra-articular disease and its severity for seronegative non-RA arthritis are unknown, probably because its lower incidence and prevalence.

SYSTEMIC INFLAMMATION AND MORTALITY

The systemic inflammatory process is a major predictor of mortality in patients with RA. Extra-articular disease confers a mortality risk ratio five times that of patients without such manifestations.² Seronegative non-RA arthritis patients with systemic involvement have an unclear lifespan compared with those without systemic disease.

NOT ONLY IGM RFS ARE INVOLVED IN SYSTEMIC DISEASE

Not only IgM RFs, but also IgG, IgA and IgE RF variants are proposed in the pathogenesis of severe RA and non-RA polyarthritis with extra-articular involvement.³⁻⁶ Seronegative arthritis may be seropositive for IgG, IgA and IgE RFs.

EXTRA-ARTICULAR MANIFESTATIONS

Extra-articular manifestations of ankylosing spondylitis are common and well defined: microscopic ileal and coecal inflammation (50% of patients),^{7,8} anterior uveitis (40%),⁹ aortic regurgitation and conduction abnormalities (9%),¹⁰ pericarditis (1%),¹¹ upper lobe lung fibrosis with reticulo-nodular opacities and cysts, bronchial and pleural thickening (1-2%),¹² renal amyloidosis (4-9%),¹³ and IgA nephropathy.¹⁴ Extra-articular disease of SAPHO syndrome (pleural effusion¹⁵⁻¹⁷) and psoriatic arthropathy (diastolic left ventricular dysfunction,¹⁸ cryptogenic organising pneumonia,¹⁹ idiopathic interstitial pneumonia with IgA nephropathy²⁰) is only presented in occasional reports. Nevertheless, this disease may be aggressive and requires a rapid differential work-up and appropriate management. Investigations for an underlying disease should not delay early corticosteroid and immunosuppressive therapy.

MECHANISMS OF SYSTEMIC DISEASE AND EXTRA-ARTICULAR MANIFESTATIONS

Systemic spread of extra-articular RFs, infectious antigens or new intrinsic or extrinsic non-infectious antigens may serve as a nidus for development of granulation

inflammatory tissue (pannus) destroying adjacent tissue. However, immune complexes containing exogenous antigens have never been detected in RA and spondyloarthropathies. Although preceding infections are common, germ-free state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats²¹ and elevated levels of IgM and IgA antibodies to *Proteus mirabilis* and IgM antibodies to *Escherichia coli* are associated with early seropositive RA.²²

Systemic involvement may implicate even late onset of inflammatory spondyloarthropathy presenting as undifferentiated arthritis, fever, loss of weight and large oedema, probably the most original presentation of arthritis specific to old males.²³

Pleuropericarditis associated with inflammatory bowel disease (IBD) is a rare extraintestinal complication.²⁴⁻²⁹ Cardiac involvement may also present as myopericarditis, conduction defects, and be complicated with disseminated intravascular coagulation.²⁵ Pericardial effusion may be asymptomatic with cardiac tamponade.²⁴ At least 29 cases of pleuropericarditis associated with IBD have been reported with good response to NSAIDs as well as corticosteroids.²⁵ Of note, this complication can also develop during remission, its diagnosis can be very difficult and a high level of suspicion should be maintained.^{27,28}

Further findings show common lung involvement in patients with SNA and RA. Bronchoalveolar lavage (BAL) was performed on 13 asymptomatic patients with SNA; (6 with peripheral psoriatic arthritis, 2 with axial psoriatic arthritis, 3 with ankylosing spondylitis, 2 with sacroiliitis).³⁰ BAL revealed a significant decrease of neutrophilic granulocytes and an increase in B lymphocytes in patients with SNA in comparison with 64 patients with rheumatoid arthritis (RA; 24 seronegative, 39 seropositive) and 15 healthy controls. Patients with SNA and RA had a significant increase of lymphocytes, especially T, T-helper and activated cells. In addition patients with RA had a significant increase of natural killer cells and lower percentage of alveolar macrophages and T-suppressor cells. Transbronchial biopsy was performed on nine patients with SNA and on 59 patients with RA. Abnormal histological features of lung tissue were observed in four out of nine patients with SNA (two with fibrosis, one with follicular lymphoid hyperplasia and one with desquamative interstitial pneumonitis). The abnormal lung histology in RA patients was more pronounced; however, the differences between SNA and RA were not significant. The data from BAL and histology suggest that the pulmonary involvement in SNA and RA is caused by an unspecified immunological process.³⁰ Pulmonary lymphocyte alveolitis in spondyloarthropathy has been reported as a subclinical disease using BAL with distal airspace cytology.³¹

The assessment of cytokines and their soluble receptors in the synovial fluid (SF) of inflammatory arthropathies may be useful in studying pathogenetic and immunoregulatory mechanisms underlying different diseases.³² The two immune arthropathies, RA and reactive arthritis (ReA), were characterised by increased SF levels of IL-12, sCD25 and of the sTNF-RII/sTNF-RI ratio compared with controls. ReA differed, however, from RA by showing lower IL-8 and IL-4 levels, higher IFN-gamma levels and a higher IL-12/IL-10 ratio, suggesting a more prevalent Th1 profile in ReA SF. The data indicate that the measurement of SF cytokines and soluble receptors may discriminate between each inflammatory arthropathy and might be useful in clinical practice.³² Cytokine 'storm' may be involved in highly active inflammation in our patients with severe systemic disease.³³ Cytokine storm or hypercytokinaemia is a potentially fatal immune reaction consisting of a positive feedback loop between cytokines and immune cells, with highly elevated levels of various cytokines.³⁴ The primary symptoms are high fever, swelling and redness, extreme fatigue and nausea. In some cases the immune reaction may be fatal.

T helper (Th) 17 cells have been implicated in the pathogenesis of psoriasis and psoriatic arthropathy (two of our patients). Interleukin (IL)-23 stimulates survival and proliferation of Th17 cells, and thus serves as a key master cytokine regulator for these diseases. In psoriasis, IL-23 is overproduced by dendritic cells and keratinocytes, and this cytokine stimulates Th17 cells within the dermis, joints or other target organs to make IL-17A and IL-22. IL-22 drives keratinocyte and inflammatory cell proliferation.³⁵ Targeting of these key cytokines is likely to lead to dramatic clinical improvement and prevention of severe systemic disease.

Most of our patients were febrile with high leucocytosis. The conventional view of the steps that lead to fever production is that they begin with the biosynthesis of pyrogenic cytokines by stimulated (pathogens or immune conflict) mononuclear phagocytes, their release into the circulation and transport to the thermoregulatory centre in the preoptic area (POA) of the anterior hypothalamus, and their induction there of cyclo-oxygenase (COX)-2-dependent prostaglandin (PG) E₂, the putative final mediator of the febrile response. A new unified model postulates that the steps in the production of lipopolysaccharide (LPS or Il-1) fever occur in the following sequence: the immediate activation by LPS of the complement (C) cascade, the stimulation by the anaphylatoxic C component C5a of Kupffer cells, their consequent, virtually instantaneous release of PGE₂, its excitation of hepatic vagal afferents, their transmission of the induced signals to the POA via the ventral noradrenergic bundle, and the activation by the thus, locally released norepinephrine (NE) of neural α_1 - and

glial α_2 -adrenoceptors. The activation of the first causes an immediate, PGE₂-independent rise in core temperature (T_c) (the early phase of fever; an antioxidant-sensitive PGE₂ rise, however, accompanies this first phase), and of the second a delayed, PGE₂-dependent T_c rise (the late phase of fever). Meanwhile-generated pyrogenic cytokines and their consequent upregulation of blood-brain barrier cells COX-2 also contribute to the latter rise.^{36,37} Many patients with psoriatic arthritis have neutrophilic and eosinophilic leucocytosis.³⁸ Isolated polymorphonuclear leucocytes (PMN) from psoriatic patients have normal concentrations of proteolytic enzymes and they have β -adrenergic receptors of normal density and affinity. PMN from psoriatic patients responded normally to the synthetic chemotactic peptide, f-Met-Leu-Phe. The chemotactic activities of sera from psoriatic patients were similar to those of normal sera. Sera from psoriatic patients enhanced chemokinesis of PMN more than normal control sera at a final concentration of 1%; no difference in chemokinetic response between psoriatic and normal sera was found at serum concentrations greater than 2.5%. This study suggests that the peripheral PMN from psoriatic patients are normal, but the sera of psoriatic patients has more chemokinetic activity for PMN than does normal serum.³⁸ Fever and leucocytosis are the first lines of innate immunity implicated in severe autoimmune disease of our patients.

CONCLUSION

SNA may be a severe disease with multiple system involvement, organ and life threatening. Non-IgM RFs, innate immune system, cytokines, cell and antibody mediated immunity, gram-negative pathogens and nonmicrobial antigens may be implicated in pathogenesis of systemic disease. High level of suspicion of extra-articular disease should always be maintained. After excluding infection early, aggressive, combined immunosuppressive therapy should be initiated for systemic manifestations of SNA.

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