Isotretinoin-induced adult onset Still’s disease

I. Leibovitch, H. Amital, Y. Levy, P. Langevitz, Y. Shoenfeld

ABSTRACT
We describe a 21-year old man who was diagnosed as having adult onset Still’s disease (AOSD) in association with isotretinoin treatment for acne conglobata. The patient was febrile, with a macular salmon pink rash, arthritis, hepatosplenomegaly, and axial lymphadenopathy. Laboratory results showed leukocytosis, mild liver dysfunction and negative rheumatoid factor and antinuclear antibodies. Isotretinoin, an orally active derivative of vitamin A, has been associated with various rheumatologic conditions such as arthralgia, myalgia, vasculitis and arthritis. The etiology of rheumatic disorders associated with retinoids is still obscure; however, it is presumed that immunomodulation by several mechanisms (such as an alteration of the cytokine balance) is probably ascribable to this interesting association.

Introduction
Retinoids are synthetic derivatives of vitamin A. They are administered primarily for dermatological conditions such as psoriasis, acne, and disorders of keratinization. Isotretinoin (13-cis-retinoic acid) is an active oral retinoid. The introduction of this drug has been a key step in the ability to treat and cure severe forms of acne resistant to other treatments, especially oral antibiotics (1). Oral isotretinoin has been known to cause diverse side effects. The most commonly reported are cutaneous side effects, but bone abnormalities manifesting as skeletal hyperostosis, seronegative spondyloarthropathies and other rheumatic conditions such as arthritis, myopathy, and vasculitis have been reported as well (2-6).

We report on a case of adult onset Still’s disease (AOSD) that was precipitated by isotretinoin treatment for acne conglobata. To the best of our knowledge this is the first report associating retinoids with this disease.

Case report
A 21-year-old man was admitted to our department due to a 3-week fluctuating spiky fever reaching 40°C, diffuse articular pain and 7 kg weight loss. The patient had noted a salmon-colored macular rash that concomitantly appeared on his trunk, neck and extremities almost every time his fever spiked and which vanished as the fever went down. Three months prior to his illness the patient was treated with oral isotretinoin due to severe acne conglobata. Although his acne greatly improved, the patient gradually developed the above mentioned symptoms. Isotretinoin was stopped only 3 weeks later and the patient was admitted to our department.

Physical examination revealed moderate hepatosplenomegaly, swollen painful joints (right elbow, wrists, metacarpal phalangial and proximal interphalangial joints) with a limited active range of movement. There was no enthesitis or tenosynovitis. A slightly enlarged, non-tender lymph node was palpated in the left axilla. During his hospital stay fluctuating fever as high as 39.5°C accompanied by increasing fatigue were noted. The patient underwent a comprehensive work-up including serological tests for EBV, CMV, Rickettsia, HIV, HBV, and HCV, which did not support a recent infection. Laboratory studies demonstrated microcytic anemia, an erythrocyte sedimentation rate (ESR) of 70 mm/1 hr, a white blood cell count of 20 - 30 x 10^9/L with 90% polymorphonuclear cells, and elevated levels of liver enzymes. Rheumatoid factor and antinuclear antibodies were not found and serum complement concentrations were normal. HLA-B27 was negative. The chest X-ray examination was interpreted as normal but an abdominal sonography, confirmed later by a CT scan, demonstrated a homogeneous enlarged liver and spleen and 2 small lymph nodes in the periporal area. A Gallium-67 whole body scan showed increased articular uptake in the small joints of the hands, feet, shoulders, and knees with a higher degree of uptake in the right elbow. No induration was detected following a subcutaneous PPD injection. After exclusion of infectious and neoplastic causes we assumed that the clinical manifestations supported the diagnosis of AOSD and prednisolone 60 mg was initiated with a rapid resolution of the symptoms and signs. Two weeks later 2 g/day salazopyrine - a second line agent
used in AOSD (7) - was added and the dosage of corticosteroids was gradually tapered. During this period there were a few occasions of arthralgia and joint swelling. After a year from his first admission, corticosteroids were stopped. Six more months later the patient is still taking salazopyrine and is enjoying a quiescent remission with this therapeutic regimen.

Discussion
AOSD is a clinical entity of unknown etiology, a variant of systemic juvenile rheumatoid arthritis in adulthood. Still was the first to describe this disease in children and adolescents in 1897. Almost a century later Bywaters reported on a similar disorder occurring in adults (8). The diagnosis is solely a clinical one and is often difficult. Clinical and laboratory features are various and not always pathognomonic. The diagnosis is usually determined by exclusion of infectious, malignant and autoimmune conditions (9-11). Yamaguchi et al. (9) advocated that major criteria consisting of fever, arthralgia, typical rash, and leukocytosis and minor criteria consisting of sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, and the absence of rheumatoid factor and antinuclear antibody may be helpful in diagnosing AOSD. Five criteria including at least 2 major ones should be met in order to establish the diagnosis of the disease (9).

Our diagnosis was supported by the fact that the patient reported fulfilled all of the above criteria. Like our patient, many others develop a typical evanescent maculopapular, salmon pink eruption (12). A sore throat might be a heralding symptom during the early stage of the disease in a significant number of patients (13). Transient arthralgia or myalgia may appear in more than 16% of patients taking isotretinoin (14).

Laboratory features are not pathognomonic. Neutrophilia, elevated liver enzymes, increased ESR and C-reactive protein (CRP), and the lack of rheumatoid factor and antinuclear antibodies are primary laboratory findings. Often a normocytic normochromic anemia may be seen, with the characteristics of anemia of a chronic inflammatory disease (12). An elevated serum ferritin concentration has been reported to be an adjunct for the establishment of the diagnosis (15, 16).

The prognosis of the disease is presumed to be basically benign (17). Complications may occur such as interstitial lung disease with pneumonitis, pericarditis, amyloidosis and, rarely, life-threatening diffuse intravascular coagulation (18, 19). Severe disease activity, liver abnormalities and consumption of anti-rheumatic drugs have been associated with the emergence of these various complications (12).

Nonsteroidal anti-inflammatory drugs, corticosteroids and methotrexate have all been implicated in the treatment of AOSD (16-20). Several communications elaborated on the role of intravenous immunoglobulins and cyclosporine A as alternatives to classical steroid therapy in patients with a refractory disease. (21, 22).

Retinoids, both naturally occurring and synthetic, are analogues of vitamin A. They act as potent immunomodulators and, in addition to their role in the treatment of acne, are used for psoriasis and other disorders of keratinization (23, 24). A new emerging role in which retinoids have been evaluated is the blockade of cancer growth (25). The all-trans-retinoic acid isomer has been previously shown to be one of the cornerstone of acute promyelocytic leukemia therapy (26).

Chronic administration of high doses of vitamin A may produce anorexia, weight loss, fever, hepatosplenomegaly, alopecia, cheilitis, elevated cerebrospinal fluid pressure, thrombocytopenia, abnormalities of serum lipid profiles, bone and joint pain and hyperostoses (14, 27). Adverse rheumatological effects of retinoids are very common, particularly when prescribed in high dosages. Their incidence may exceed 80% after a few years of administration (28). The most common of these adverse effects of isotretinoin are arthralgias or myalgias appearing in more than 20% of patients on the drug (4). The pathogenic mechanism is not clear. It has been hypothesized that isotretinoin might induce lysosomal membrane solubilization that causes destruction of synovial cells, thus rendering joints sensitive to mechanical injury (4). Other rheumatologic manifestations such as arthritis, myopathy, and vasculitis may also appear (2-4). To the best of our knowledge AOSD has never been associated with the administration of isotretinoin or any other retinoid. In our reported case, the alternative possibility of a mere coincidence is an option that could not be excluded.

Several immunomodulatory effects of isotretinoin have been reported. Isotretinoin was shown to inhibit in vitro secretion of type 1 cytokines (IFN-gamma, GM-CSF, IL-2) on the one hand and to enhance the synthesis of IL-6 and IL-2 receptor on the other (29-31). These findings may be of interest because recent studies have shown that IL-6 and other cytokines are significantly elevated in patients with AOSD (32, 33), as well as having a role in the pathogenesis of anemia in chronic rheumatoid arthritis and juvenile chronic arthritis (34, 35).

Other studies suggest that retinoids can increase the percentage of peripheral blood lymphoid cells expressing surface markers for T-helper cells and cause significant alterations in natural killer cell activity (36, 37).

The fact that retinoids are widely used nowadays makes it obligatory to rule out AOSD, especially when the patient appears with classic features of the disease. Having a dramatic onset with the potential for significant consequent morbidity (occasionally even fatalities) these patients should be treated appropriately when the diagnosis is confirmed. The possible role of cytokines in the pathogenesis of rheumatological diseases may shed light on future strategies of treatment.

References
5. DE FRANCESCO V, STINCO G, CAMPANELLA M: Acute arthritis during isotretinoin treatment for acne conglobata [letter]. Dermatology
CASE REPORT

1997; 194: 195.