Erdheim-Chester Disease: An Orphan Condition Seeking Treatment

Roei D. Mazor BMedSc[1,3]*, Anat Kesler MD[2] and Yehuda Shoenfeld MD FRCP[1,3]

[1]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
[2]Neuro-Ophthalmology Unit, Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: Erdheim-Chester disease (ECD), histiocytosis, hairy kidney, interferon-(IFN), interleukin-1 (IL-1)

IMAJ 2012; 14: 388-389

Erdheim-Chester disease is a rare form of non-Langerhans cell histiocytosis, originally described as "lipid granulomatosis" by Jakob Erdheim and William Chester in 1930. This disease is characterized by the infiltration of CD68(+) and CD1a(-) histiocytes to various target organs and tissues. The resulting effect is the formation of xanthomatosis or xanthogranulomatosis with or without associated fibrosis. These processes eventually impair the function of critical organ systems. Among the more common sites of involvement are the bones, central nervous system and retro-orbital space, cardiovascular system, lungs and pleura, kidneys and retroperitoneum, and the skin. Patients who suffer from the multisystemic form of ECD face a grim prognosis.

Over the past decade, ECD became better recognized by medical professionals around the world [1]. As clinical suspicion became more frequent, more patients were diagnosed and the number of ECD cases reported in the medical literature increased substantially. This vigorous outburst of case reports provided fertile ground for basic research. In an attempt to better understand the enigmatic pathogenesis of this disease, researchers began to elucidate the numerous facets of the biology of ECD.

Whether ECD represents a monoclonal or a reactive process remains unclear, as reflected in the conflicting data of recent studies [2-5]. ECD seems to be associated with an intense TH1 immune response. Arnaud and colleagues [6] described a unique cytokine signature in ECD patients consisting of increased levels of interferon-alpha, interleukin-12, monocyte chemotactic protein-1 (MCP1/CCL2) and decreased levels of interleukins 4 and 7. Additional findings were the expression of tumor necrosis factor-alpha and IL-6 and 8 in the ECD lesion [7]. Others described the expression patterns of chemokines and their corresponding receptors in ECD [8]. One special focus of interest was the role of IL-1 in the pathogenesis of ECD. Both Tran et al. [9] and Aouba et al. [10] described the successful treatment of ECD patients with a recombinant IL-1 receptor antagonist. Another focus of interest was the roles of IL-6 and TNFα in the pathogenesis of ECD. Many of the teams mentioned above [6,7,9,10] found these cytokines to be overexpressed in ECD. IL-6 is thought to play a pivotal role in the osseous involvement of ECD [11]. Despite this, no attempt to treat ECD patients with anti-interleukin-6 antibody therapy was ever reported in the medical literature. These facts are similar with regard to TNFα signaling and ECD since only one patient was ever reported to be treated with anti-TNFα antibody therapy. Another patient, who was brought to our knowledge by means of a personal communication, was treated successfully with anti-TNFα antibody. To date, IFNα remains the most efficacious agent to treat ECD. It was recently found to be an independent predictor of survival [12]. Little data exist regarding the efficacy of alternative treatments.

In this issue of *IMAJ*, Asher et al. [13] present a 49 year old male with ECD. This particular case exemplifies how elusive the diagnosis of ECD can be, as this patient did not present with the classical characteristic bone pain. The diagnosis was made mainly due to recognition of the "hairy kidney" appearance on computed tomography. In addition, this case validates the beneficial effects of IFNα in the treatment of the retroperitoneal involvement of ECD.

Several factors contribute to the correct diagnosis and management of a complex ECD patient. As seen in the patient mentioned above, a high level of clinical suspicion is one. Among the others, and equally important, is the concept of a "governing" physician. Since ECD often manifests as a multisystem disease, an ECD patient requires the surveillance of several specialists. In such cases, careful coordination and broad management by an experienced physician would improve the quality of surveillance and, consequently, of patient care.

*MD candidate class of 2015

ECD = Erdheim-Chester disease

IL = interleukin

TNFa = tumor necrosis factor-alpha

IFNa = interferon-alpha

Corresponding author:
Dr. Y. Shoenfeld
Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-8070, **Fax:** (972-3) 535-2855
email: shoenfel@post.tau.ac.il

References

1. Haroche J, Arnaud L, Amoura Z. Erdheim-Chester disease. *Curr Opin Rheumatol* 2012; 24 (1): 53-9.
2. Al-Quran S, Reith J, Bradley J, Rimsza L. Erdheim-Chester disease: case report, PCR-based analysis of clonality, and review of literature. *Mod Pathol* 2002; 15 (6): 666-72.
3. Tsai JW, Tsou JH, Hung LY, Wu HB, Chang KC. Combined Erdheim-Chester disease and Langerhans cell histiocytosis of skin are both monoclonal: a rare case with human androgen-receptor gene analysis. *J Am Acad Dermatol* 2010; 63 (2): 284-91.
4. Chetritt J, Paradis V, Dargere D, et al. Chester-Erdheim disease: a neoplastic disorder. *Hum Pathol* 1999; 30 (9): 1093-6.
5. Vencio EF, Jenkins RB, Schiller JL, et al. Clonal cytogenetic abnormalities in Erdheim-Chester disease. *Am J Surg Pathol* 2007; 31 (2): 319-21.
6. Arnaud L, Gorochov G, Charlotte F, et al. Systemic perturbation of cytokine and chemokine networks in Erdheim-Chester disease: a single-center series of 37 patients. *Blood* 2011; 117 (10): 2783-90.
7. Dagna L, Girlanda S, Langheim S, et al. Erdheim-Chester disease: report on a case and new insights on its immunopathogenesis. *Rheumatology (Oxford)* 2010; 49 (6): 1203-6.
8. Stoppacciaro A, Ferrarini M, Salmaggi C, et al. Immunohistochemical evidence of a cytokine and chemokine network in three patients with Erdheim-Chester disease: implications for pathogenesis. *Arthritis Rheum* 2006; 54 (12): 4018-22.
9. Tran TA, Pariente D, Lecron JC, Delwail A, Taoufik Y, Meinzer U. Treatment of pediatric Erdheim-Chester disease with interleukin-1-targeting drugs. *Arthritis Rheum* 2011; 63 (12): 4031-2.
10. Aouba A, Georgin-Lavialle S, Pagnous C, et al. Rationale and efficacy of interleukin-1 targeting in Erdheim-Chester disease. *Blood* 2010; 116 (20): 4070-6.
11. Wilejto M, Abla O. Langerhans cell histiocytosis and Erdheim-Chester disease. *Curr Opin Rheumatol* 2012; 24 (1): 90-6.
12. Arnaud L, Hervier B, Neel A, et al. CNS involvement and treatment with interferon-alpha are independent prognostic factors in Erdheim-Chester disease: a multicenter survival analysis of 53 patients. *Blood* 2011; 117 (10): 2778-82.
13. Asher I, Ranibovith I, Katz M, Sthoeger Z. Erdheim-Chester disease in a 49 year old man. *IMAJ Isr Med Assoc J* 2012; 14: 401.

Capsule

In need of nutrients for gastrointestinal infections

Gut pathogens such as *Esherichia coli* and *Salmonella* are faced with several hurdles when trying to establish an infection: the recruitment of immune cells, the secretion of antimicrobial factors, and competition in the form of the billions of commensal bacteria that normally reside in our guts. As a result, the pathogens need to have a few tricks up their sleeve. Liu et al. report on one such example, used by *Salmonella enterica* serovar *Typhimurium*, a pathogen that causes severe gastroenteritis in humans. In response to *S. typhimurium* infection, neutrophils are recruited to the gut in mice and produce the antimicrobial protein calprotectin. Calprotectin functions by sequestering essential metals, such as zinc, thus limiting an important nutrient source for the invading pathogen. *S. typhimurium* can overcome this and compete with the commensal flora, however, because it expresses a high affinity zinc transporter. Strains that lacked this transporter did not grow as well in the inflamed gut but were not at a disadvantage in the absence of inflammation. These results suggest that nutrient availability is a key factor in the establishment of gastrointestinal infections.

Cell Host Microbe 2012; 11: 227

Eitan Israeli

Capsule

Relationship between disease activity and type 1 interferon in dermatomyositis and polymyositis

Greenberg et al. report on 24 patients with dermatomyositis (DM) or polymyositis (PM) who were followed for up to 6 years (mean 1.9 years) at 2–7 follow-up visits while receiving standard clinical care. Clinical data and blood samples collected at 80 patient visits were used for the analysis of cytokine-induced gene expression for the signaling pathways of type 1 interferon (IFN), tumor necrosis factor-α, interleukin (IL)-1β, granulocyte-monocyte colony-stimulating factor, IL-10 and IL-13. A type 1 IFN signature score, but not other cytokine signature scores in the blood of patients with DM or PM, correlated highly with disease activity, decreased significantly with immunomodulatory therapies and showed concordant changes with major changes in disease activity. Type 1 IFN signature score in the blood correlates with disease activity in longitudinal follow-up of individual patients with DM or PM. The type 1 IFN-inducible gene transcripts in the blood have potential utility for monitoring disease activity in patients with DM or PM.

Genes Immun 2012; 13: 207

Eitan Israeli

Clinical Efficacy and Adverse Effects of Golimumab in the Treatment of Rheumatoid Arthritis

Aluma Chovel-Sella MD BSc, Rebekah Karplus MD, Tal Sella MD and Howard Amital MD MHA

Department of Medicine B, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: Golimumab is a fully human monoclonal antibody targeting tumor necrosis factor-alpha (TNFα), an important cytokine in the pathogenesis of rheumatoid arthritis (RA) and other arthritides. Golimumab was approved for the treatment of rheumatoid arthritis with methotrexate (MTX) and with or without MTX for psoriatic arthritis and ankylosing spondylitis. Administration is by monthly subcutaneous injection. In this review we present some of the major clinical trials evaluating the efficacy of golimumab with or without concomitant MTX in RA patients, including patients resistant to previous biologic treatments. In addition, we collected data on safety and adverse effects encountered in clinical trials. Current data show golimumab to be an effective and safe choice for the treatment of various inflammatory arthritides.

IMAJ 2012; 14: 390-394

KEY WORDS: tumor necrosis factor (TNF), golimumab, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA)

Rheumatoid arthritis is an autoimmune disease manifesting primarily as an inflammatory arthritis. It is associated with chronic inflammation of synovial joints, mostly hands and feet, as well as systemic extraarticular inflammation. The disease is progressive, and over time patients develop joint destruction and bone erosion that eventually leads to personal and vocational disability [1-3]. The impact on individual patients and on society is high, since impaired health can be life-long and significantly reduces both quality of life and function [3-5]. The pathophysiology of the disease involves the overproduction of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukins-1 and 6 [6,7].

TNFα plays a key role in driving inflammation not only in RA but also in other immune-mediated diseases such as ankylosing spondylitis, psoriatic arthritis and inflammatory bowel diseases [6-9]. It elicits the production of other pro-inflammatory cytokines and adhesion molecules, increases endothelial layer permeability and, consequently, increases leukocyte recruitment into the involved joint. TNFα upregulates osteoclasts and metalloproteinases, inducing bone erosion [7,10]. In the past decade, numerous drugs targeting TNFα have been developed due to this pivotal role in the pathophysiology of many rheumatologic diseases. Infliximab, etanercept and adalimumab have all proven effective in the treatment of RA, dramatically ameliorating clinical manifestations, reducing joint damage and radiographic progression, and inducing remissions [11,12]. TNFα inhibitors are biological agents with significant disease-modifying effects [13].

Other treatment options for rheumatoid arthritis include the older non-disease-modifying antirheumatic drugs, such as prednisolone and non-steroidal anti-inflammatory drugs and the widely used non-biological DMARD methotrexate. However, their potential toxicity and suboptimal efficacy prompted the development of additional treatment options. Aside from the anti-TNFα drugs already mentioned, other newly available biological agents target the IL-1 receptor (anakinra), the co-stimulatory molecule, CD28 (abatacept), the IL-6 receptor (tocalizumab) and B cells (rituximab).

Anti-TNFα drugs include two subtypes, antibodies to TNFα and fusion proteins consisting of a TNFα receptor coupled with the Fc domain of human immunoglobulin G1, Etanercept (Enbrel®, Immunex Pfizer, USA). Infliximab (Remicade®, Janssen Biotech, USA) is a chimeric monoclonal anti-TNFα antibody. Adalimumab (Humira®) Abott Laboratories, USA), Certolizumab pegol (Cimzia®, UCB, USA) and golimumab (Simponi® Janssen Biotech, USA) are fully human anti-TNFα monoclonal antibodies [Table 1] [7-9,14,15].

WHAT IS GOLIMUMAB?

Golimumab is a TNFα inhibitor that binds to the specific receptors of both transmembrane and soluble TNFα and blocks their action. Golimumab was approved in April 2009 by the U.S. Food and Drug Administration for the treatment of moderate to severe RA with MTX, and for use with or without

TNFα = tumor necrosis factor-alpha
RA = rheumatoid arthritis
DMARD = disease-modifying antirheumatic drugs
IL = interleukin
MTX = methotrexate