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Erdheim-Chester's Disease of the Heart: A Diagnostic Conundrum and Collision with the Same Mass in the Orbit

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ABSTRACT

Erdheim-Chester's disease is a rare multisystem xanthogranulomatosis, afflicting the skeletal system with the occasional involvement of soft tissues. We delineate an unusual case of a cardiac variant of Erdheim-Chester's disease presenting with pericardial effusion and as a collision with a synchronous orbital manifestation. We describe our diagnostic pathway and propose a novel treatment option involving nonsteroidal anti-inflammatory drugs. The role of cyclo-oxygenase in the disease process and inhibition thereof by NSAIDs is hypothesized and discussed.

INTRODUCTION

Erdheim-Chester's disease (ECD) is a form of histiocytic granulomatosis, afflicting the skeletal system and various inner organs. This rare lipoidosis predominantly affects the metaphyses and diaphyses of the long bones. Lipid-laden histiocytes have also been described in the pericardium, cardiovascular system, lungs, mediastinum, pleura, liver, spleen, small bowel, kidneys, adrenal glands, basal forebrain, retroperitoneum, skin, pelvis, and orbits.

In 1930, the pathologist Chester and his mentor Erdheim described the first 2 cases of ECD as lipoid granulomatosis [Chester 1930]. Up to 42% of patients with ECD are asymptomatic; the disorder in these patients is incidentally discovered on radiographs or cross-sectional imaging studies obtained for other reasons. However, up to one third present with systemic signs and symptoms. The median age of the patients is in the sixth decade, and there is a slight male preponderance [Kenn 1999].

Pericarditis, pericardial effusion and heart failure are associated with ECD, and perivascular fibrosis involving the whole aorta (referred to as the "coated aorta") and anterior iliac arteries has been documented [Serratrice 2000]. However, a review of patients with ECD reported no instances of diffuse and extensive myocardial involvement in patients with pericarditis or heart failure, although myocardial and pericardial biopsies and autopsies were performed in some of these patients [Veyssier-Belot 1996]. Nevertheless, some reports delineate negligible focal myocardial invasion, yet ECD in these cases has not "really" involved the myocardium; instead of myocardial infiltration, extensive epicardial fibrosis, invasion and obstruction of coronary arteries, subepicardial fat tissue thickening, and microscopic foci of myocardial infiltration were present in these cases [Haroche 2004].

Histologic findings of ECD are similar to those of Langerhans cell histiocytosis (LCH) with an infiltration by foamy histiocytes, surrounded by fibrosis and irregularly thickened bone trabeculae. They differ, however, from LCH in the lack of intracytoplasmatic Birbeck granules (also called X-bodies) on electron microscopy and negative immunostaining for protein S100 [Devouassoux 1998].

Histiocytes are defined as immune cells, arising from $CD34^+$ progenitors in the bone marrow, and include several cell types, which can be divided into 2 groups according to their immunohistochemical characteristics. The first subset of histiocytes derives from the monocyte-macrophage group and includes monocytes, macrophages, and Kupffer cells of the liver. The second group derives from the Langerhans cell–dendritic cell group and is the histiocytic cell type involved in histiocytosis X, now referred to as LCH [Cline 1994; Veyssier-Belot 1996]. The spectrum of histiocytic disorders is very broad, and an exact distinction between the

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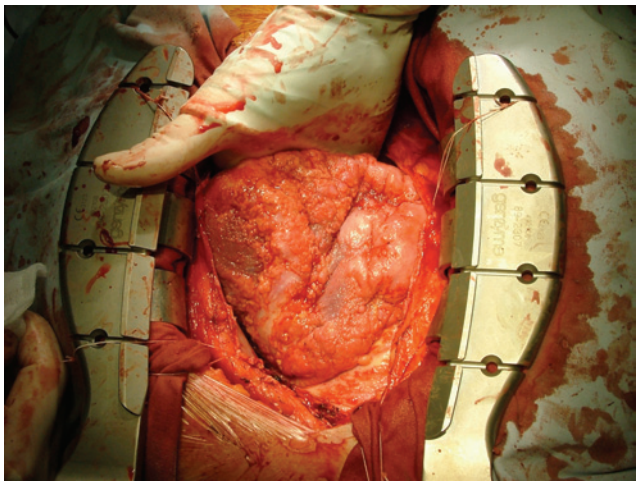

Figure 1. Intraoperative finding delineating an enlarged heart with a verrucous lesion infiltrating both ventricles, the right atrium, and the ascending aorta.

maladies is not available. Classifications can be made on immunohistochemical typing of the histiocytic cell, biological behavior (benign or malignant), or clinical syndromes. It has also been proposed that the pathogenesis of ECD is based on a primary macrophage cell disease [Devouassoux 1998].

Here we present a case of ECD with atypical myocardial involvement with orbital manifestation, and delineate an unusual diagnostic and therapeutic conundrum.

CASE DESCRIPTION

A 57-year-old Caucasian man with a history of hypertension, multifocal ischemic stroke, orbital pseudotumor, and gastro-esophageal reflux disease (GERD) presented to the emergency department with a 10-day history of progressive dyspnea and malaise. The patient also complained of increasing chest discomfort for 2 weeks.

Relevant History and Findings

Two months before admission, the patient developed progressive dyspnea with exertion and accelerating symptoms of fatigue associated with nonproductive cough. At that time, a transthoracic echocardiogram revealed a small-to-moderate sized pericardial effusion, but no evidence of tamponade physiology. The patient was treated with conventional therapy, including ACE-inhibitors, β-blockers, and diuretics. In addition, he was on proton-pump inhibitors for GERD, antiplatelet drugs, and nootropics.

On arrival and upon admission in the emergency department, the patient's blood pressure was 115/65 mmHg. His heart rate was 95 beats/min and his respiratory rate was 18 breaths/min with an oxygen saturation of 96% while breathing room air. He was mildly agitated. On physical examination, no upper torso cyanosis was appreciated. Neck examination demonstrated moderate jugular venous distension to the angle of his jaw when he was sitting upright. Cardiac auscultation revealed mild tachycardia with gently diminished heart sounds. Pulmonary examination was remarkable for basilar crackles and diminished breath sounds at the right lung base. Dullness to percussion and bronchial breathing were also noted over the angle of the left scapula (Ewart's sign). The patient's lower extremities had mild pitting edema bilaterally.

He was noted to have a right-sided exophthalmos, mild dysarthria, clumsy hand movements, and right-sided weakness with gait and limb ataxia. Focal findings included right facial paralysis, bilateral pronator drift, right upper extremity hemiparesis (4/5), and paresthesia with bilateral Babinski responses.

Chest x-ray on admission revealed a markedly enlarged cardiac silhouette consistent with pericardial effusion. Absence of pulmonary vasculature in the hilum and a right-sided pleural effusion was also appreciated. Electrocardiography was notable for sinus tachycardia and low QRS voltage. An echocardiogram revealed a large pericardial effusion without evidence of pericardial tamponade. Emergency pericardiocentesis without catheter placement was performed at the bedside under echocardiographic guidance, and 600 mL of serous fluid was evacuated from the pericardium with immediate clinical improvement in his symptoms. Analysis of pericardial fluid showed 2 easily discernable cell populations with more distinct mesothelial and histiocytic features without evidence of atypia.

Further diagnostic workup included computed tomography (CT) and magnetic resonance imaging (MRI) examination of the chest, which demonstrated pericardial fluid without evidence of a mass lesion. He was scheduled for elective cardiovascular MRI (CMR). In the meantime, however, his clinical status gradually deteriorated and semi-emergency operative exploration was performed, including pericardial fenestration and biopsy without tumor debulking. The verrucous lesion (Figure 1) had infiltrated the anterior wall and most parts of the right ventricle, the right atrium, and the ascending aorta, and was not amenable to complete resection. Immediately after the intervention, however, the patient's symptoms resolved completely.

The open-heart biopsy revealed foamy histiocytes nested among polymorph granuloma, fibrosis, and xanthogranulomatosis compatible with ECD. This diagnosis was confirmed by immunohistochemical investigations of the histiocytes, showing negative results for CD1a and S100 protein without evidence of atypia (Figure 3A).

Past Medical History

The patient had a history of bilateral orbital (retrobulbar) infiltration associated with right-sided exophthalmos for at least 2 years without signs of visual loss or diplopia. CT and MRI scans demonstrated a 2.6-cm enhancing mass in the right, and 1.4-cm lesion in the left orbit (Figure 2). No invasion of the optic nerve was present. There was no evidence of bony erosion. The paranasal sinuses were clear. The orbital infiltrate on the right side had undergone a biopsy 1 year before the presentation of the patient at our center. The histologic diagnosis at that time revealed chronic inflammation with polymorphous lymphocytic infiltrate with no evidence of malignancy, consistent with idiopathic inflammatory pseudotumor. Therapy of oral prednisone 20 mg daily was initiated with mild resolution of the mass within a few weeks. His exophthalmos, however, recurred as the oral steroids were tapered to 5 mg daily. An intralesional injection of 25 mg of triamcinolone into the pseudotumor was performed. Clinical

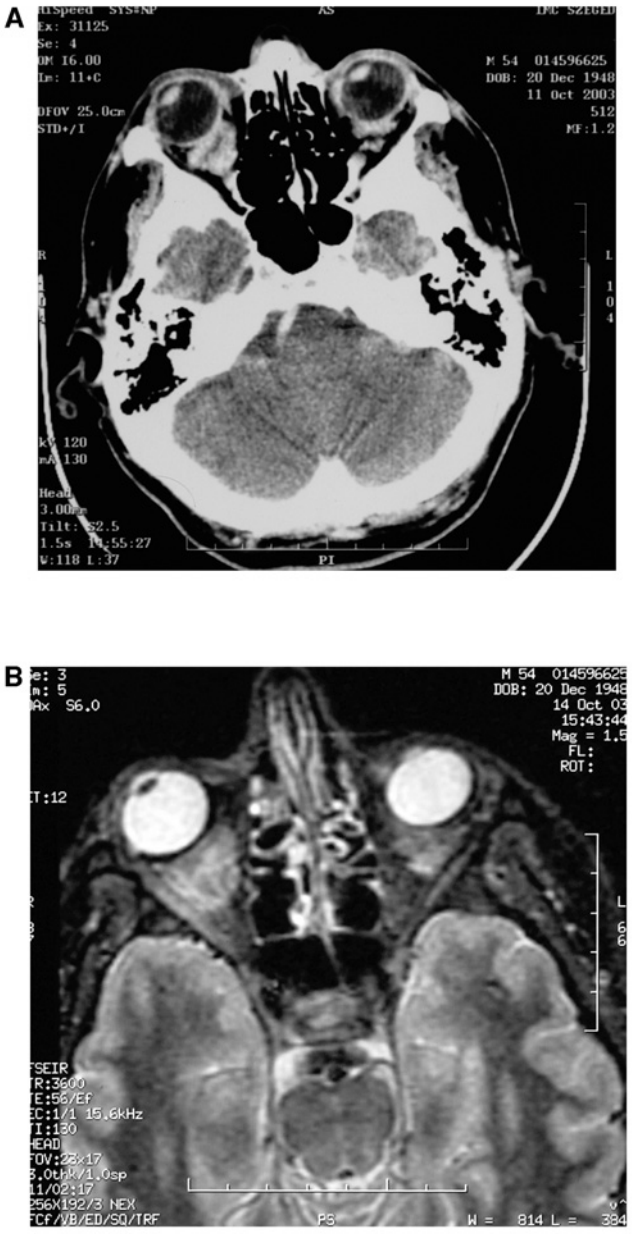

Figure 2. Radiological evaluation of the exophthalmos. CT (A) and MRI (B) scans show retrobulbar mass in both orbits.

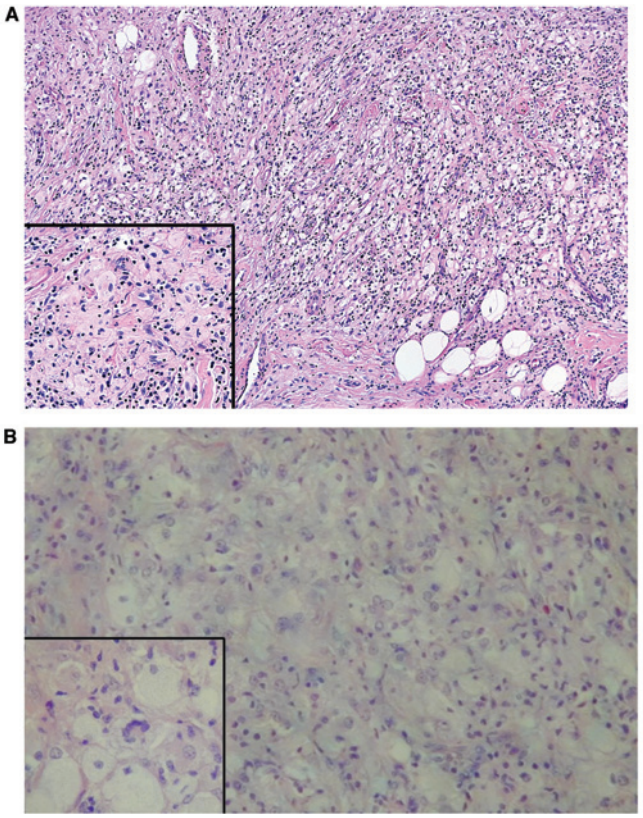

Figure 3. Histopathological evaluation of the biopsies from the heart (pericardium) (A) and orbit (B). Sections stained with hematoxylin and eosin (H&E), and photographed at an orginal magnifcation of 10× and 40× (A and B, respectively), are densely infiltrated by large, foamy macrophages (histiocytes). Inset: macrophages have round-to-oval nuclei and pale cytoplasm (H&E, orginal magnifcation of 40× and 100×, respectively). Immuno-histochemical evaluation of samples from both heart and orbit shows positivity for CD68, and complete negativity for S100 and CD1a.

resolution again occurred for 4 weeks' duration with subsequent recurrence. He developed Horner's syndrome, and examination disclosed 0.25 vision in the right and 1.0 vision in the left eye. Subsequent findings included normal intraocular pressure, normal anterior chambers by slit-lamp, Hertel 30-24/104 mm, and CFF 24/34 Hz. CT and MRI images taken at that time were notable for marked progression of the mass (right: $3 \times 3 \times 3.5$ cm, left: 2.5 cm).

He then underwent an orbital decompression surgery to decrease the amount of exophthalmos, to minimize his symptomatology, and to re-evaluate histopathologic characteristics of the mass. A concurrent bone marrow biopsy was also performed due to the suspicion of a neoplastic process, specifically lymphoma. On subsequent examinations after surgery, the exophthalmos decreased by 3 mm and the right visual acuity improved to 0.8.

The removed specimen was fixed in 4% formaldehyde solution and processed for pathological examination. Microscopic examination showed multiple foci of histiocytes admixed with a variable number of plasma cells, lymphocytes, and a few eosinophils. Touton and other giant cells could not be detected. Paraffin-embedded sections were subjected to standard immunohistochemical protocols. Immunohistochemically, the histiocytes were S100 negative and were strongly positive for CD68 (a macrophage marker), with diffuse, cytoplasmic staining. All cells were negative for CD1a, a Langerhans cell marker. There was no evidence of lymphoma. Connective tissue disease workup, including antinuclear antibody (ANA) and antinuclear cytoplasmic antibody (ANCA) levels, was nondiagnostic. The bone marrow demonstrated normal cellularity. A presumptive diagnosis of orbital xanthogranuloma was made. High dose oral prednisone therapy of 80 mg daily was initiated with mild resolution of the lesion.

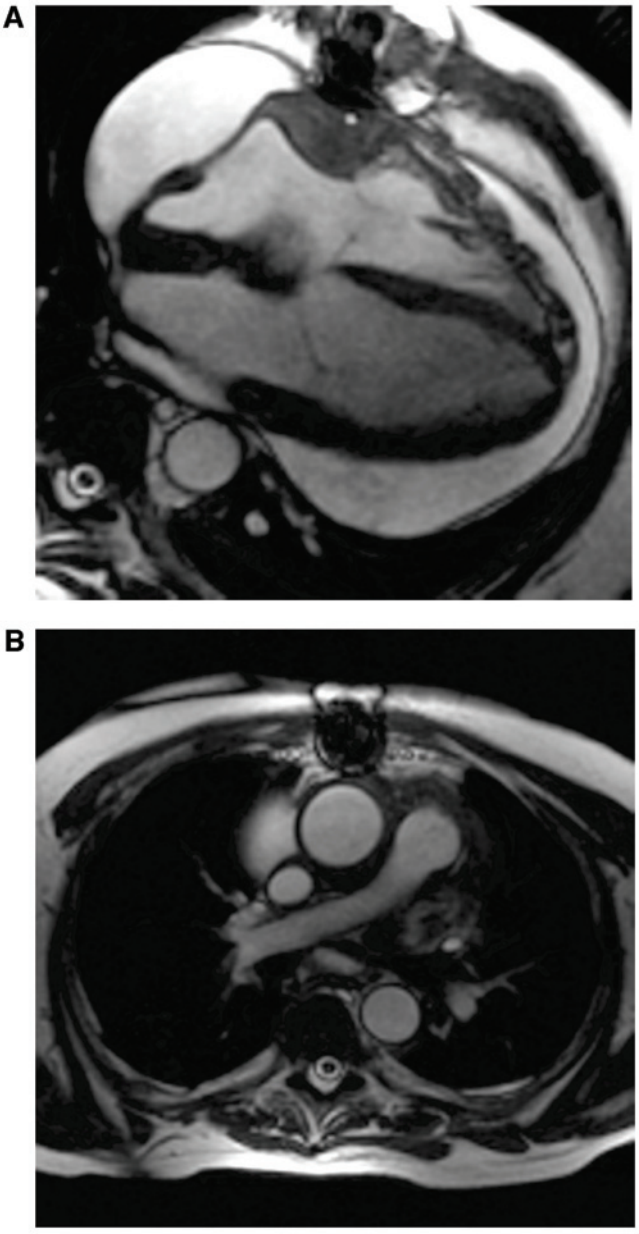

Figure 4. CMR scan of the heart reveals: A, extensive right ventricular involvement of ECD. The lesion also infiltrates the anterior wall of the left ventricle, the intra-atrial septum, and the right atrium without extra-cardiac invasion, as shown in this four-chamber scan. B, Transverse image at the level of the aortic root and pulmonary trunk demonstrates marked thickening of the walls of the great vessels ("coated aorta sign").

Synergy of the Two Diseases: The Same Lesion?

No sooner had a presumptive diagnosis of ECD of the heart been made, the pathologic slides from orbital biopsy were available for review, and confirmed the diagnosis. A periodic acid-Schiff (PAS) stain showed strong positivity in the cytoplasm of the histiocytoid cells. Immunostains performed in a block from the primary tumor in the orbit and in another block from the heart with the histiocytoid proliferation showed identical findings. There was strong cytoplasmic positivity of the histiocytoid cells for CD68, and complete negativity for S100 and CD1a. The tissues were fixed in Karnovsky's fixative (2% paraformaldehyde, 2.5% glutaraldehyde in 0.1 M cacodylate buffer at pH 7.4) and processed for embedding in epoxy resin. Thin sections (70-80 nm) were examined with transmission electron microscopy. Electron-dense intracytoplasmic (Birbeck) granules were not seen in the histiocytes. As such, pathologic re-evaluation of the specimens revealed ECD both in the heart and in the orbit (Figure 3).

The diagnostic workup continued with CT and MRI examination of the brain, chest, abdomen, and pelvis. While his brain CT was positive for previous ischemic stroke with multifocal areas of infarction and bilateral pseudotumor of the orbit, scans also revealed lipid deposits in the diploe of the skull. The results of CT and MRI scans of other body cavities were reported as normal. Results of CMR of the heart revealed pericardial effusion along with an enhancing mass within most parts of the right ventricle and in the anterior wall of the left ventricle. Involvement of the atrial septum and the right atrial wall without tumor-like intraluminal spreading was also observed. Marked thickening of the walls of the aortic root and pulmonary trunk was present ("coated aorta sign"). No extra-cardiac lesions were identified (Figure 4).

A ^{99m}Tc-labeled hydroxyl-methylene-diphosphonate (^{99m}Tc-HDP) bone scintigraphy showed increased signal intensity in the sternum and several ribs, the mark of the sternotomy with associated mechanical lesions in the costae. Increased tracer uptake, consistent with ECD, was found in the proximal epiphyses of both tibiae, in the distal epiphyses and metaphyses of both femurs, and mild focal increases were observed in both humeri, radii, and in the skull (Figure 5).

Workup by the hematology/oncology service, performed to rule out malignant neoplasms of the lymphoid system, was unremarkable. Full endocrinological assessment included non-nodular euthyroid (colloid) goiter and right gynecomastia. Blood tests showed normal lipid profile.

An alternative therapeutic trial of local irradiation of the right orbit (44Gy) was attempted with mild symptomatic improvement. The patient gradually developed cardiac failure due to restrictive cardiomyopathy on grounds of ECD. He subsequently received a course of celecoxib (Celebrex; Pfizer, New York, NY, USA), a nonsteroidal anti-inflammatory drug (NSAID) with selective type-2 cyclo-oxygenase (COX_2) inhibitory activity, with marked resolution of symptoms, and was listed for cardiac transplantation.

DISCUSSION

ECD is a rare, non-inherited, potentially fatal, disseminated multisystem xanthogranulomatous infiltrative disorder of unknown origin associated with a characteristic pattern of symmetric osteosclerosis of the metaphyseal regions of long bones and infiltration in other organs by foamy histiocytes. This skeletal manifestation was clearly demonstrated in our patient by bone scintigraphy.

Involvement of soft tissues is also common in ECD. About half of affected patients have extraskeletal manifestations, which can include involvement of the hypothalamus/posterior

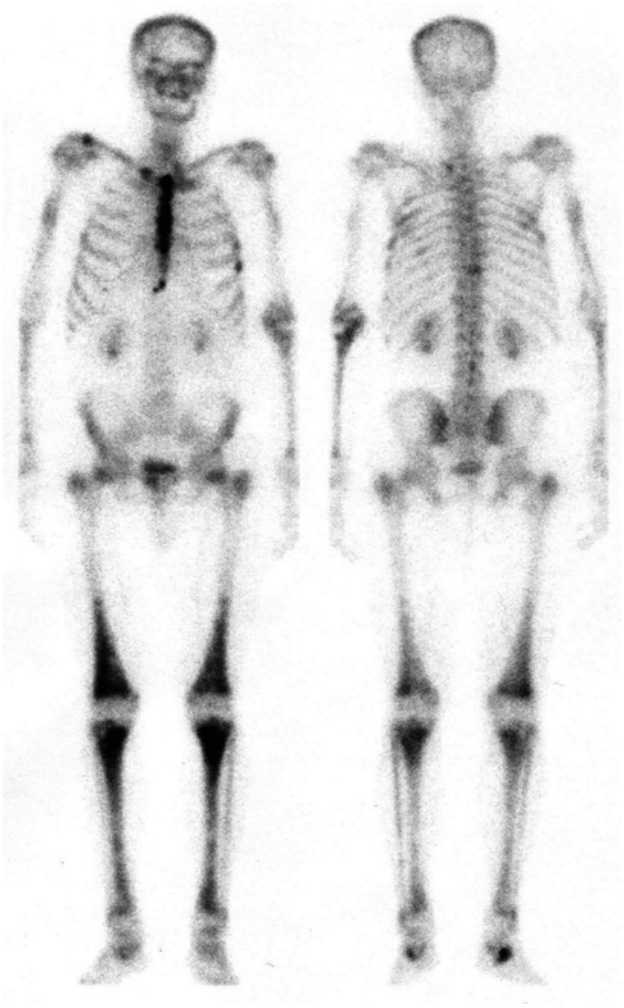

Figure 5. ^{99m}Tc-HDP bone scan showing symmetrically increased tracer uptake in the tibiae and femurs; mildly increased signal intensity is present in the humeri, radii, and skull.

pituitary, orbit, retroperitoneum, skin, lung, and cardiovascular system, often leading to a classic triad consisting of central diabetes insipidus, sclerotic bone lesions, and exophthalmos. Even though involvement of the aorta and pericardium has been described in ECD [Veyssier-Belot 1996; Haroche 2004], profound myocardial manifestation was an unusual finding in our case, let alone colocalizing in the orbit presenting as a unique duet.

Histopathologically, the foamy histiocytes are different from Langerhans cells and specific for histiocytosis X (or LCH), because they have no intracytoplasmic Birbeck granules (X bodies) and do not immunostain for S100 protein [Devouassoux 1998].

Apart from clinical manifestation and histological evaluation, diagnostic tools are scarce. Disturbed lipid homeostasis has also been suggested for ECD to yield lipid-laden histiocytes. Diploic lipid deposit in the skull, however, is also an extraordinary finding. As such, lipid profiling may be used to support the diagnosis of ECD, even though our patient had a normal lipid pattern. Also, a positive bone scan may enhance the recognition of subtle radiographic changes in the skeletal system.

It is difficult to assess the response to therapy of ECD, given its rarity. Steroids, radiation therapy, surgery, and chemotherapy have all been attempted, with variable results. Likewise, the exact prognosis is unknown. Very few successful treatments have been described for ECD with orbital involvement. Previously reported ineffective forms of therapy include high-dose corticosteroids, radiation therapy, and various chemotherapeutic and immunomodulatory agents, including interferon-α [Petrikowski 2000]. Interestingly our patient tolerated high-dose NSAID with rapid resolution of symptoms. However, the mechanism by which nonsteroidal agents might exert such a favorable effect in ECD is not known.

The most important mechanism of NSAID-action is to inhibit COX, which is a key enzyme in the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxane, all potent mediators of inflammation. COX-independent mechanisms involve inhibition of phosphodiesterase; this leads to potentiation of PGE_1-mediated increased intracellular cAMP-levels and subsequent inhibition of proinflammatory cellular functions, peripheral blood lymphocyte responses to mitogen stimulation, neutrophil and monocyte migration,

and various neutrophil functions. NSAIDs also inhibit activation of the transcription factor NF-κB. Other cell-signaling molecules, such as mitogen-activated protein (MAP) kinases and the transcription factor AP_1, may also be modulated by these agents. These effects may not only play a role in the inhibition of neutrophil phagocytic and adhesive activity, but also efficiently inhibit histiocytic functions, thus exerting a beneficial effect in ECD.

Because tumor-infiltrating macrophages express high levels of COX, and given the known link between COX_2 and cell growth, proliferation, and carcinogenesis, it may be postulated that this enzyme plays a role in the progression of various tumors. Indeed, COX_2 has been identified as a key target for chemo-prevention in many human neoplasias [Shiff 1999]; this may also hold true for ECD. As such, we hypothesize that COX_2 expression might be significantly related to long-term patient survival in ECD. Collectively, our data theoretically demonstrate a reduction in the incidence of ECD lesions and volume with inhibition of the COX_2 enzyme.

Our novel NSAID-approach, therefore, might shed new light on ECD management. The literature contains little data regarding COX_2 expression in histiocytes, nor are there epidemiologic or clinical data suggesting an ECD-inhibitory effect of aspirin or NSAIDs. This may be due in part to the infrequency of this malady. Nevertheless, given the insensitivity of these unpredictable lesions to radiotherapy and conventional chemotherapy, and the "partial" response to steroids, COX-inhibitors may possibly be beneficial in this setting. Along with the putative role of COX-inhibitors in ECD, the use of COX_2-based treatments as adjuvant therapy will be of growing interest. To evaluate the beneficial role of COX_2-inhibitors, monitoring COX_2 levels in ECD histiocytes, along with their response to NSAIDs, and studies performed on larger cohorts of ECD patients are necessary.

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