Indomethacin for Recurrent Cutaneous Necrotizing Eosinophilic Vasculitis

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Recurrent cutaneous necrotizing eosinophilic vasculitis (RCNEV) is a rare disease characterized by clinical features of pruritic purpuric papules and angioedema. Skin biopsies revealed the eosinophil-predominate necrotizing vasculitis affecting small dermal vessels. Systemic corticosteroid is a very effective treatment. There are many side effects associated with systemic corticosteroid therapy. The authors report a case of RCNEV successfully treated with indomethacin. To the authors' knowledge, there has been no reported case of RCNEV treated with indomethacin.

Keywords: *Indomethacin, Recurrent cutaneous necrotizing eosinophilic vasculitis, Treatment*

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Case Report

A 53-year-old white male presented with a 6-year history of recurrent pruritic papules, nodules, and ulcers of the face, scalp, and hands. He had pulmonary tuberculosis when he was 4 years old. He had no history of asthma. The skin biopsy showed focal necrosis of the epidermis, collagen fibers, subcutaneous tissue, and the hair follicles. There was a dense mixed inflammatory cell infiltrate, consisting of lymphohistiocytes, numerous eosinophils and extra vasated red blood cells around these necrotic areas (Fig. 1). In some areas, the collagen fibers were coated with eosinophilic granules. Many small blood vessels in the dermis showed necrosis of the endothelial cells. There were fibrin thrombi and deposition of eosinophilic fibrinoid material in the vascular lumens and walls, respectively (Fig. 2). There were numerous eosinophils and lymphohistiocytes infiltrate around these small blood vessels. There was no leukocytoclasis. The diagnosis of recurrent cutaneous necrotizing eosinophilic vasculitis(RCNEV) was made. His evaluation was normal or negative for the following tests: complete blood cell count; urine analysis; stool examination; antinuclear antibody; anti neutrophillic cytoplasm antibody; rheumatoid factor; erythrocyte sedimentation rate;B1C; C4; C-reactive protein; cryoglobulin; hepatitis B and C serologic studies; VDRL; and anti HIV antibody. Bacterial culture from the skin revealed *Staphylococcus epidermidis*. Cultures for fungus and mycobacteria were negative. Chest X-ray showed a small calcified spot at the left upper lung. He was treated with 60 mg of prednisolone daily with good response. Last year he developed the pruritic and purpuric papule lesion on left forearm after discontinuation of systemic corticosteroid for a few months. Indomethacin was commenced at a dosage of 75 mg daily with a little improvement. Subsequently it was increased to 150 mg daily. He responded very well in 1-2 weeks while omeprazole 20 mg daily was also given to prevent gastrointestinal side effects.

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Discussion

RCNEV was first described in 1994 by Chen et al[1]. It is a distinct entity characterized by glucocorticoid - responsive pruritic, purpuric papules, and angioedema of face and hands. Skin biopsies revealed necrotizing vasculitis of the small vessels of the skin,

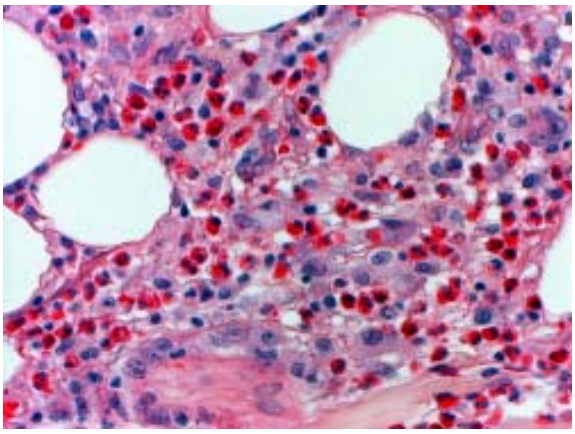

Fig. 1 The infiltrate consists of lymphohistiocytes and numerous eosinphils around the blood vessels and between collagen bundles in the upper and deep dermis as well as subcutaneous tissue (H&E, x40)

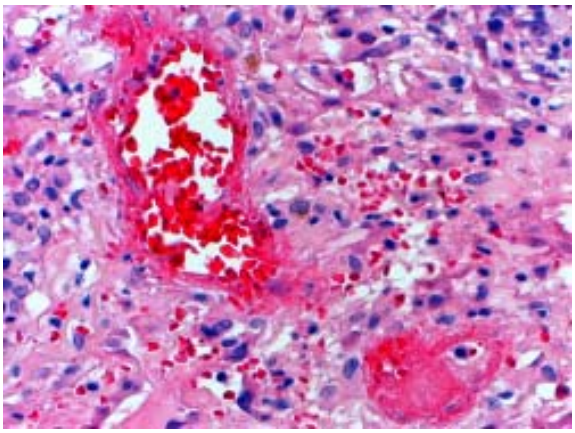

Fig. 2 High magnification shows a perivascular mixed inflammatory cell infiltrate and deposition of fibrinoid material and fibrin thrombi in the walls and lumens of many small vessels in the upper and deep dermis (H&E, x20)

with exclusively eosinophilic infiltration and minimal or no leukocytoclasis[2]. It is idiopathic but may be associated with hypereosinophilic syndrome, connective tissue diseases (Felty's syndrome, rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome) and Kimura's disease[3-5]. In the presented case, there was no associated disease identified.

A pathogenic relationship between eosinophils and vasculitis in RCNEV was studied[1,4]. Endothelial destruction was found in the presence of degenerated eosinophils and free eosinophil granules. Striking deposition of the cytotoxic eosinophil granules was found in an affected wall. Eosinophil granule protein such as major basic protein (MBP) and eosinophil peroxidase were toxic to endothelial cells in a dose-dependent manner. Marked MBP deposition in the areas of vessel damage strongly suggested that eosinophils contributed to or caused the damage.

The treatment of choice is systemic corticosteroid. Nevertheless, the disease commonly occurs in the nature of recurrent attacks. Sulphatast tosilate and dapsone were also used in combination with systemic corticosteroid[5,6]. Sulphatast tosilate has been used in the treatment of various atopic conditions such as eczema and asthma. It is known to suppress not only Ig E synthesis, but also the production of interleukin (IL)-4 and IL-5.

Indomethacin is one of the non-steroid anti-inflammatory drugs (NSAID). It has been used in many dermatoses including urticarial vasculitis and eosinophilic pustular folliculitis (EPF or Ofuji's disease)[7]. Millns et al reported a series of ten patients with urticarial vasculitis who were treated with indomethacin[8]. Nine of these patients achieved either complete or partial resolution of their illness during therapy with indomethacin. Gastrointestinal irritation was the only side effect noted.

The first successful treatment of a patient with EPF with indomethacin was reported by Hosokawa in 1984[9]. Reports of successful treatment of EPF with oral indomethacin have been replicated in Thailand and Singapore[10,11]. Ota et al recommended indomethacin as a first choice of treatment for EPF[12]. The mechanism of indomethacin is not well understood. It is a potent cyclooxygenase inhibitor. It is thought that certain cyclooxygenase arachidonic acid metabolites are chemotactic factors for eosinophils, neutrophils, lipids, and prostaglandins. Indomethacin decreases the local production of these arachidonic acid-derived chemotactic factors, which are thought to play a role in the pathogenesis of EPF[9].

Any combination of effects may have played a role in the beneficial outcome of indomethacin therapy in the presented patient. In summary, the authors reported a rare case of RCNEV successfully treated with indomethacin. Since there are fewer side effects particularly in comparison with those of corticosteroid, it should be used for treatment of RCNEV.

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การรักษาโรค Recurrent cutaneous necrotizing eosinophilic vasculitis ด้วยเอ็นโดเมทาซีน

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โรค Recurrent cutaneous necrotizing eosinophilic vasculitis (RCNEV) เป็นโรคการอักเสบของเส้นเลือดชนิดอีโอสิโนฟิล ที่พบได้น้อย มีลักษณะทางคลินิก เป็นตุ่มนูนคัน และบวมที่ผิวหนัง ลักษณะทางพยาธิวิทยาจะพบการอักเสบของเส้นเลือดเล็ก ๆ มีเซลล์อีโอสิโนฟิลเป็นลักษณะสำคัญ การรักษาในปัจจุบัน คือ การใช้ยาคอร์ติโคสเตอรอยด์ชนิดรับประทาน ซึ่งอาจมีผลข้างเคียงได้มากมาย เพราะโรคนี้มักเป็น ๆ หาย ๆ ผู้นิพนธ์ ได้รายงานการรักษาโรค RCNEV ด้วยยารับประทานเอ็นโดเมทาซีนได้ผลดี ยานี้ได้มีการสืบค้นทางเอกสารและรายงานการวิจัยต่าง ๆ ผู้นิพนธ์พบว่ายังไม่เคยมีรายงานการรักษาโรค RCNEV ด้วยเอ็นโดเมทาซีนมาก่อนซึ่งยาชนิดนี้มีผลข้างเคียงที่น้อยกว่ายาในกลุ่มของคอร์ติโคสเตอรอยด์