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Suppression of Erythema nodosum by Indomethacin

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Abstract. Erythema nodosum (EN) can be a debilitating illness. Many treatment modalities have been suggested but none is universally effective. We describe three patients with severe EN secondary to streptococcal pharyngitis who were unresponsive to large doses of aspirin. Following the administration of indomethacin in doses of 100 to 150 mg per day, all three showed a dramatic response, with prompt resolution both of systemic symptoms and of local signs of inflammation. The lesions of EN involve the lower cutis, with inflammation of septae and fat lobules. It is likely, therefore, that the local liberation of fatty acids leads to increased prostaglandin synthesis which, in turn, is responsible for the intense inflammation. The impressive suppression of EN by indomethacin could be related to the inhibition of prostaglandin synthetase in the subcutaneous fatty tissues.

Key words: Erythema nodosum; Indomethacin

Although frequently severe and debilitating, erythema nodosum (EN), is usually self-limited, re-

solving within 3–6 weeks (1, 2). A number of medications have been employed, but none has been found to be universally satisfactory (1).

We have observed 3 patients with severe, debilitating EN secondary to an antecedent streptococcal pharyngitis, who responded promptly and dramatically to indomethacin. Our experiences, reported here, suggest that indomethacin be used in the treatment of this disorder and further imply a possible mechanism for the local inflammatory process of EN.

CASE REPORTS

Case 1. R. G., a 57-year-old Mexican-American female, was admitted to the hospital with an acute febrile illness of 2 days' duration. She complained of numerous painful, red, raised lesions on all extremities. Ten days prior to the onset of her acute illness, she had had a sore throat and received oral penicillin. She had taken penicillin numerous times in the past without complications. On physical examination the patient was acutely ill, with an oral temperature of 101°F and numerous tender EN lesions, most prominently over the ankles, dorsum of the feet, the wrist and the dorsum of both hands, with underlying edema, perarticular inflammation and tenosynovitis. The pertinent abnormalities from an extensive laboratory evaluation were an elevated ESR of 128 mm/h, and an ASO titer of 500 Todd units. Treatment initially consisted of aspirin 4 g/day in divided doses. On the 4th hospital day, the plasma salicylate concentration was 17.1 mg/dl. Disability due to EN with fever persisted and new lesions developed daily. On the 6th hospital day, aspirin was discontinued and indomethacin was given in a dose of 50 mg t.i.d. Within 12 hours, the patient dramatically improved. Inflammation of the skin and joints had markedly subsided. Twenty-four hours after the initial indomethacin dose, a new nodule was noted, but it was minimally inflamed and non-tender. No new lesions developed subsequently. With the onset of treatment, she became afebrile. Indocin was continued for 2 weeks. There was no recurrence of EN.

Case 2. B. S., a 34-year-old white female, had a sore throat which subsided untreated and was followed in 4 days by migratory polyarthralgias and the development of painful red nodules on the extremities. She had taken oral contraceptives containing estrogen for 3 years. On admission to the hospital, the patient had the classical dermal lesions of EN and synovitis of joints proximal to the EN lesions. Abnormal laboratory findings were a leukocytosis of 15900/mm³, ESR 60 mm/h, positive CRP and throat culture positive for Group A streptococci. Her ASO titer was initially 166, increasing to 500 Todd units.

Initially, she was considered to have acute rheumatic fever and received benzathine penicillin and large doses of aspirin. Even though her plasma salicylate levels equalled or exceeded 30 mg/dl, joint complaints persisted and new EN lesions developed. On the 4th hospital day, aspirin was discontinued and indomethacin started in

a dose of 50 mg t.i.d. Twenty-four hours later she was objectively improved and erythema of existing lesions had diminished. Although a new EN nodule developed within 24 hours, it was minimally tender. No additional new lesions developed and existing nodules showed prompt and total resolution within a further 24 hours. The patient was discharged with instructions to continue indomethacin for 2 weeks. There was no recurrence.

Case 3. M. V. 30-year-old Mexican-American female, had an upper respiratory infection with pharyngitis followed in 3 weeks by inflammation over the left pretibial area. Originally considered to have "cellulitis", she received erythromycin. She did not improve and painful red lesions developed on the right pretibial area, and she was admitted to the hospital. She had taken oral contraceptives for 2 years. On examination, the patient had extensive EN lesions on both lower extremities. The ESR was 35 mm/h and the ASO titer rose from 166 to 333 Todd units during her hospitalization. Numerous other laboratory studies proved normal. Initially treated with bed rest, elevation of the extremities and aspirin 4 g/day, there was only mild improvement. On the 4th hospital day, new lesions developed and aspirin was therefore discontinued and indomethacin given in a dose of 25 mg i.d. Her response was prompt and complete, with subsidence of the inflammatory nodules. After 2 weeks, indomethacin was discontinued and there was no recurrence of EN.

DISCUSSION

Although usually self-limiting, EN can be a debilitating disorder. The constitutional symptoms, together with inflammation of the involved extremities including tenosynovitis and arthritis, can be severe. Of the numerous drugs suggested for this illness, none is universally successful (1, 2). Potassium iodide is thought to be effective in some cases, but prolonged treatment is required (one month) to prevent a recrudescence (3). Although EN can respond dramatically to corticosteroids, it is not likely that this form of treatment will shorten the course of the disorder (4); signs and symptoms reoccur when the corticosteroid dose is decreased or discontinued (4-6). In addition, this form of treatment should be avoided if the underlying cause of EN is unknown or if due to an infection.

In each of the 3 patients we studied, aspirin in doses sufficient to be anti-inflammatory was ineffective. The development of new inflammatory lesions continued. Following the initiation of indomethacin treatment, there was definite resolution of existing nodules within 12-24 hours, and complete subsidence thereafter in each of the 3 patients. EN lesions did not recur when indomethacin was discontinued. Thus, this drug provided prompt

relief in a disorder that usually requires 3-6 weeks to subside.

An antecedent streptococcal pharyngitis could be documented in each of our 3 patients and was presumed to be the cause of the EN. Whether indomethacin will be beneficial in the treatment of EN due to diseases other than streptococcal pharyngitis is not known, but the histopathological changes of EN are common to all disorders with which it is associated (7). Therefore, it is likely that indomethacin will prove to be beneficial in all.

The exact pathogenetic mechanisms responsible for the development of EN are uncertain. A local, delayed hypersensitivity response and localization of circulating immune complexes have been implicated (7-9). Whatever the cause, the histopathologic changes are well recognized. The intense inflammatory reaction in the deep layers of the cutis involves subcutaneous fat septae. We reasoned that the intense local inflammatory reaction could be due to prostaglandin release. Inflammation and necrosis of fat would lead to the release of fatty acids which, in turn, would serve as precursors for prostaglandin synthesis. If this were the case, then an inhibitor of prostaglandin synthetase should be beneficial in the treatment of EN. Indomethacin is a potent inhibitor of this enzyme (10) and was therefore used and found to be suppressive. Aspirin, a very weak inhibitor of prostaglandin synthetase, was without effect.

It is surprising that this is the first reported experience of indomethacin in the treatment of EN. The drug has been shown to be beneficial for EN leprosum (11). However, this disorder is etiologically and histologically distinct from non-leprosy EN (1, 2).

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Excessive Cerumen Production Due to the Aromatic Retinoid Tigason in a Patient with Darier's Disease

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Abstract. A patient with Darier's disease is described, who developed excessive cerumen production and otitis externa in addition to general symptoms of adverse effects during treatment with the aromatic retinoid Tigason.

Oral vitamin A and topical vitamin A acid have been used to treat skin diseases with abnormalities of keratinization such as psoriasis ichthyosis and Darier's disease, but their use has been limited by their toxicity.

More recently the oral aromatic retinoid analogue of vitamin A (Ro-10-9359: Tigason) has been used for the same conditions, with good results (2-4). A limiting factor regarding the therapeutic use of retinoids is the frequency of side effects, most often cheilitis, mucosal dryness, exfoliation of palms and soles, pruritus, sweating, alopecia and severe liver damage, as well as general malaise, dizziness, nausea, etc.

This paper describes a patient with Darier's disease who developed excessive cerumen production resulting in otitis externa and loss of hearing during Tigason treatment, in addition to general symptoms.

CASE REPORT

A 35-year-old woman with a history of Darier's disease since the age of 6, was first seen as an out-patient in June 1979. From 3rd August, treatment was started with Tigason 75 mg daily until mid-September. She responded well, with almost total normalization of her skin, but suffered from adverse effects such as dry mouth and lips, and an intolerable feeling of deafness. Examination revealed excessive cerumen and otitis externa bilaterally.

The treatment was discontinued for 3 months, but the disease worsened, and Tigason treatment was started again, first with 75 mg daily for 2 weeks, then 50 mg daily. Her condition improved, but after 6 weeks' treatment she again developed a feeling of deafness and discharge from the ears. She also complained of general malaise, dizziness and nausea, and stopped the Tigason treatment.

There was a new recurrence of Darier's disease and several kinds of topical treatments were tried, but with little or no effect. She was admitted to hospital in August 1981 to try Tigason therapy once more. Before treatment was instituted, her ears were examined by an otolaryngologist, cerumen was removed and an audiogram proved normal.

After one week of medication the patient felt tired, complained of nausea, vertigo and general malaise, and the treatment had to be discontinued. A new audiogram failed to reveal any change, but quite a considerable amount of cerumen had already been produced.

DISCUSSION

Excessive production of cerumen and the development of otitis externa during Tigason treatment are not well known adverse effects. Burge et al. (1) mention in their study of 18 patients with Darier's disease treated with Tigason, that 2 patients complained of 'blocked ears'. Tsambaos & Orfanos (5) stated that after 2 weeks of treatment with oral retinoid, guinea pigs developed erythema, edema and scaling of the skin, with the changes most pronounced at the ear and snout.