Progressive pigmentary purpura related to raloxifene

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ABSTRACT

Progressive pigmentary purpura is a rare condition characterized by lymphocytic capillaritis histologically causing various clinical entities which are also named as persistent pigmented purpuric dermatoses. It is generally idiopathic; however, rare cases secondary to drugs and various diseases have been reported. In this report we describe a case of progressive pigmentary purpura induced by raloxifene, a selective estrogen receptor modulator which is primarily used in the treatment and prevention of postmenopausal osteoporosis. As far as we know, no case of progressive pigmentary purpura has previously been reported as an adverse effect of raloxifene.

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Progressive pigmentary purpura (PPD), also known as persistent pigmented purpuric dermatosis, capillaritis and idiopathic pigmented purpuric eruption, is a group of rare diseases characterized by orange-brown pigmentation and non-palpable purpura localized especially on the lower limbs.[1,2] Histologically perivascular lymphocytic inflammation (lymphocytic capillaritis) without fibrinoid necrosis in the small vessel walls, hemorrhage and epidermal changes are observed.[3] There are 8 clinical variants known as Schamberg disease, purpura annularis telangiectodes (Majocchi's purpura), purpuric pigmented lichenoid dermatitis (Gougerot-Blum disease), eczematid-like purpura of Doucas and Kapetanakis, itching purpura (disseminated pruriginous angiodermatitis), lichen aureus, unilateral linear capillaritis, and granulomatous pigmented purpura. However, the term of PPD is usually preferred since clinical features usually cannot be limited in these variants and clinical overlap between the various subtypes may occur.[1,3] Raloxifene hydrochloride (Evista ®) is a selective estrogen receptor modulator (SERM) primarily indicated in the treatment and prevention of postmenopausal osteoporosis. Its biological effects are carried out by binding to the estrogen receptors with high affinity and arranging gene expression. The most frequent adverse effects related to raloxifene include hot flushes, diaphoresis, peripheral edema, venous thrombosis, mastodynia, vaginitis, and myalgia.[4] To our knowledge, no case of raloxifene induced PPD has been reported previously. We report herein a case of raloxifene induced PPD which improved by stopping the usage of the drug, and reappeared after oral challenging the same drug.

Case Report. A 50-year-old woman who had been using raloxifene for the treatment of postmenopausal osteoporosis presented with a 2 week-history of an asymptomatic eruption located on the lower limbs. The eruption appeared after 4 weeks of beginning raloxifene. There was no history of another illness or usage of any drug. Physical

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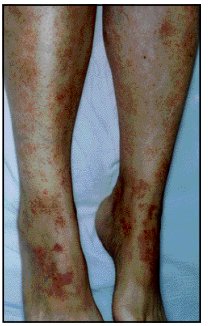

Figure 1 - Progressive pigmentary purpura located on the pretibial regions and the backs of the feet.

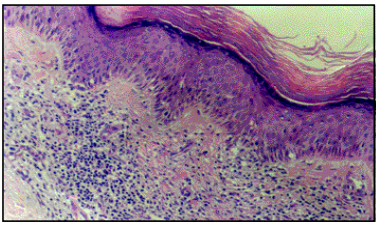

Figure 2 - Photomicrograph showing orthokeratosis, focal vacuolar degeneration of the basal layer, perivascular lymphocytic infiltrate and extravasated erythrocytes in the upper dermis (Hematoxyline and eosine X 100).

examination revealed non-blanching, reddish-brown purpuric macules and patches and hyperpigmentation irregularly distributed on the pretibial regions and dorsa of the feet (**Figure 1**). Histological examination of punch biopsy material revealed orthokeratosis, focal vacuolar degeneration in the basal layer, dermal perivascular mononuclear cell infiltration and erythrocyte extravasation (**Figure 2**). Systemic examination was normal. There were no abnormalities among the laboratory tests including complete blood cell count, erythrocyte sedimentation rate, prothrombin time, bleeding time, liver function tests, serum glucose and lipid levels. Serological test results are also normal. The diagnosis of PPD was made with these clinical and histological findings, and she was advised to stop raloxifene and was given a lotion containing 5% urea and a topical steroid of moderate potency. The eruption gradually faded within the following 4 weeks. When all the lesions were healed, the patient was given raloxifene again to confirm whether it was the culprit agent. Because the lesions reappeared after 20 days of oral challenge, raloxifene was definitely established as the causative agent.

Discussion. The etiological factor remains mostly unknown in cases of PPD. However sometimes hepatic, hematologic, endocrine, connective tissue diseases, infections, contact materials and drugs have been accused.[1,2] Drugs may cause PPD by either allergic or toxic mechanisms. Thiamine propyldisulfide, pseudoephedrine, aspirin, meprobamate, acetaminophen, carbromal, ampicillin, pefloxacin, carbamazepine, furosemide, lorazepam, glipizide, barbiturates, medroxyprogesterone acetate, chlordiazepoxide, nitroglycerin, trichlomethiazole, topical 5-fluorouracil and interferon-α are among the reported drugs associated with PPD.[1,2,5-7] The elapsed time between the initiation of the responsible drug and the appearance of the eruption is variable, it can be weeks or years.[5] Wang et al[7] reported a case of PPD in which the eruption began on the fourth day of infliximab infusion for the treatment of Crohn's disease and recurred when the drug was used again after it healed. However, the eruption occurs usually several weeks or months after beginning the drug.[5,6]

There are different hypotheses about the pathogenesis of PPD. One of them implicates the effects of gravity and elevated venous pressure as well as a disturbance or weakness of the cutaneous blood vessels leading to capillary fragility and erythrocyte extravasation, since the lesions predominantly occur on the lower limbs and buttocks. However, this does not explain the inflammatory infiltrate which is common in these disorders. It has also been postulated that Langerhans-cell mediated injury, and immune-complex deposition results in capillary leakage. Some immunofluorescent studies have shown vascular deposition of C3, C1q, IgM or IgA. However, these deposits have not been shown in most cases.[3,8] An examination of each subtype of the disease with a panel of immunophenotypic markers such as intercellular adhesion molecule 1 (ICAM-1), ymphocyte function-associated antigen 1 (LFA-1) and endothelial leukocyte adhesion molecule 1 (ELAM-1) revealed an infiltrate composed of CD1a+ cells and CD3+/CD4+ T lymphocyte irrespective of the histologic pattern. This suggests a common pathogenesis of vascular damage in the setting of a localized cell-mediated immunologic reaction, similar to allergic contact dermatitis.[3]

Gupta et al[6] suggested that drugs may act as a hapten and cause an antigen-antibody complex which accumulates in the endothelial cell and produces vascular damage resulting in the symptoms of PPD.

The disease is mostly seen among middle-aged male adults. The course is chronic but usually benign. However, progression to cutaneous T cell lymphoma has been observed in some treatment-resistant cases.[9] There is no consistently successful therapy for PPD. Topical and systemic steroids, ascorbic acid, pentoxifylline, oral rutoside, antihistamines, supporting socks, CO_2 snow, and in the resistant cases stanozolol, griseofulvin, psoralen+ultraviolet A (PUVA) and cyclosporine have been used with variable success.[1,2]

Raloxifene is a SERM derived from benzothiophene. Since it prevents bone resorption by stimulating osteoblastic activity like the other SERM tamoxifen, it has been increasingly used for the treatment of postmenopausal osteoporosis in recent years. The SERMs have additional favorable effects on lipid profiles and the incidence of second breast cancers, and unfavorable effects on the incidence of venous thrombosis and hot flushes. While tamoxifen increases the risk of endometrial cancer, raloxifene does not, since it has been shown to act as an estrogen agonist on bone density but as an estrogen antagonist on breast and uterine tissue.[4,10] We performed a detailed literature search and found no PPD or any cutaneous side effect due to raloxifene, except the aggravation of systemic lupus erythematosus reported only in one case.[10] Since our patient is the first case, to our knowledge, of PPD definitely induced by raloxifene, we find it valuable to report. We suggest that the addition of PPD to the list of the known side effects of raloxifene would be appropriate.

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