

PLASMA CELL GRANULOMAS IN NON-LIPEMIC XANTHOMATOSIS: APPARENT INDUCTION BY INDOMETHACIN

Walter B. Shelley and Howard M. Rawnsley

From the Departments of Dermatology and Pathology (William Pepper Laboratory), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Abstract. A 71-year-old man with non-lipemic, generalized, plane xanthomas developed nodules and tumors within one month of starting indomethacin therapy. These enlarged and spread during 5 months of daily indomethacin but promptly and spontaneously involuted when the indomethacin was discontinued. Within 4 months, the nodules and tumors were completely gone. The process is viewed as an "indoderma", i.e. a granulomatous drug reaction, analogous to an iododerma.

Key words: Plasma cell; Granuloma; Xanthomatosis; Indomethacin; Drug reactions; Tumors

Generalized plane xanthoma is a rare, photographically elusive, yet rather unforgettable disease. The lesions are, as it were, giant xanthelasma covering vast areas of skin, at times draping the entire shoulders and back with a yellow shawl. And like xanthelasma, the process seems to be a local proliferation of the superficial reticulo-endothelial system, with fat-loaded perivascular histiocytes as the singular histologic finding. Lipemia, and cholesterolemia, so characteristic of the common xanthomas, are not generally found (1). Rather, the linkage is with increased immunoglobulins in the serum (14), and as many as a third of the patients with plane xanthomas are believed to have multiple myeloma (5). The bone marrow shows an increase in plasma cells, which here and in the skin may account for the paraproteinemia (6).

It was thus with considerable interest that we observed the rapid development of plasma cell-rich nodules and tumors in widespread plane xanthomas of 18 years duration. The following outlines how we were able to interrelate the plane xanthomas, trauma, and indomethacin with these plasma cell growths.

CASE REPORT

This 71-year-old male, when first seen in September 1973, gave a history of having developed nodules and tumors of his waist, neck and wrist in May 1973. These had enlarged over the summer despite a variety of topical steroids, but remained asymptomatic. A biopsy elsewhere had revealed a granulomatous and xanthomatous reaction in the corium that was difficult to classify histopathologically.

The patient had always been in good health except for emphysema and arthritis. For the past 18 years he had noted widespread areas of his skin were yellow. His drug history revealed that from April through August 1973 he had taken indomethacin (25 mg, b.i.d.) for relief of arthralgia. Aside from aspirin, he denied having taken any other medication. Intake of bromides and iodides was specifically denied.

The most striking findings on general physical examination were those of the skin. At the belt line, on both sides of the abdomen, were reddish masses extending over a 6×8 cm area and elevated 1 to 2 cm above the skin surface. The central areas were firm and purplish yellow in color. There were no pustules, erosions or ulcers, but rather the lesions appeared firm and infiltrative. Similar but less prominent plaques were seen on the upper anterior chest, and on the inner aspects of both wrists.

The patient had giant xanthelasmic lesions of his eyelids which extended down onto the cheeks, and a yellow infiltrate involved all of the furrows of his face. Much of the entire chest and back were of a light yellow hue which became obvious only by contrast at the margin of this yellow infiltrate. The axillae were exempt but nearly all other intertriginous or furrowed sites such as the interdigital spaces, were similarly infiltrated with this yellow material.

A biopsy of the tumor of the abdominal skin showed an extensive, heavy lymphocytic infiltrate of inflammatory cells with a marked predominance of plasma cells (Figs 1, 2). These plasma cells were mature and rather uniform in appearance. Some multinucleate giant cells were present. Many aggregates of histiocytes with foamy cytoplasm were found in the upper dermis. The picture was interpreted as a reactive plasma cell granuloma of unknown nature, occurring at a site of plane xanthoma. A biopsy of the macular yellow lesions which extended virtually over the entire chest, ab-



Fig. 1. Tumor appearing in area of plane xanthoma after one month of indomethacin therapy. Granulomatous inflammatory infiltrate of round cells and numerous plasma cells. ($\times 40$.)

domen, and back showed widespread aggregations of histiocytes in the upper dermis (Fig. 3). Their foamy cytoplasm proved to be filled with fat, as demonstrated by Sudan IV staining. The histologic pattern was considered characteristic for that of a plane xanthoma or xanthelasma.

During the course of observation, the following studies were within normal limits: complete blood count, glucose, calcium, phosphorus, alkaline phosphatase aminotransferases, lactic dehydrogenase, hydroxybutyrate dehydrogenase, cholesterol, triglycerides, carotenes and routine urinalysis. Serum lipoprotein studies showed a normal alpha, prebeta and beta pattern and no chylomicra were seen. Repeated serum protein electrophoretic studies for one year consistently showed a stable paraprotein in the fast gamma region. It represented 32% of the total protein and on immunoelectrophoresis appeared in the IgG band. The IgA and IgM bands were present and of normal thickness. By use of monospecific antisera, the IgG paraprotein could be identified as of the lambda type. Cryoglobulins or pyroglobulins were not found. No evidence of increased light chains (Bence Jones) could be found in multiple concentrated urine specimens. The serum paraprotein was repeatedly visualized as a lipid-paraprotein complex on lipoprotein electrophoresis.

Bone marrow examination revealed an increase in the number of plasma cells present (approximately 10%), but the cells were normal in appearance and were not viewed as evidence of multiple myeloma. A chest film and a bone survey showed no abnormalities.

Immunofluorescent studies of frozen sections of a biopsy of the yellow macular lesions showed no deposition of antibodies or complement in the foam cells. Immunodiffusion studies using the Ouchterlony double diffusion technique failed to reveal an antibody activity of the patient's IgG paraprotein against a lipoprotein or indomethacin.

A closed patch test on sacrificed xanthelasmic skin, using indomethacin powder, failed to induce any reaction when observed over a period of a month.

As a result of the initial studies a presumptive diagnosis of an indomethacin-induced granuloma was made and treat-

ment limited to withdrawal of indomethacin. Within one month, definite shrinkage of all of the nodules and tumors was apparent. Nothing was used systemically or topically, and within 3 months later the infiltrative lesions had eventually disappeared, leaving no scar or trace. The yellow infiltrates in the skin, however, remained unchanged as they had been for nearly 20 years. The patient was observed subsequently for over two years, with no recurrence of the tumors. Nor was there any change in his clinical plane xanthomas, his paraproteinemia, or his general health.

DISCUSSION

Within a month of beginning indomethacin therapy this patient noted the appearance of localized inflammatory growths. During the subsequent 5 months of daily oral indomethacin, the lesions progressively enlarged to become gross nodules and tumors. Within a month of stopping the indomethacin and without treatment, the growths began to involute spontaneously, and by 4 months had almost completely disappeared. In the absence of any other explanation, we have viewed the nodules and tumors as being due to a remarkable sensitivity to indomethacin.

Although the severity of the process and its tangential relationship to multiple myeloma precluded definitive testing by oral challenge, the role of the indomethacin would seem similar to that of iodides or bromides in the evocation of the granulomatous reactions. Indeed, the similarity prompted us to call our patient's problem an "indo-derma", analogous to an iododerma or bromoderma.

In the iododerma the histologic reaction has some

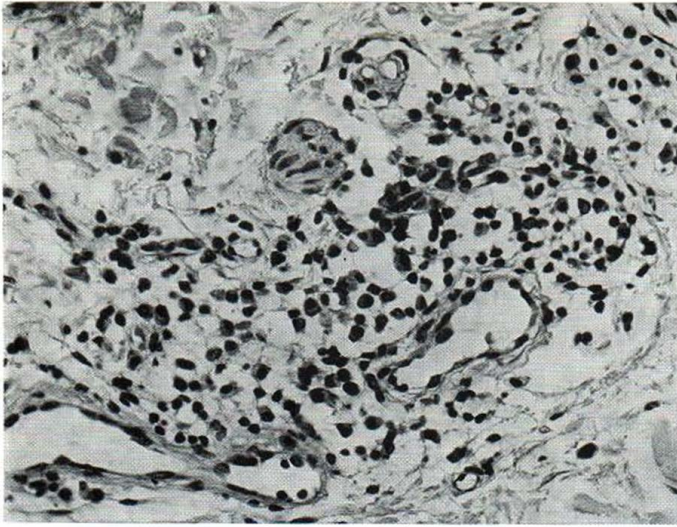


Fig. 2. Plasma cell infiltrate in granulomatous tumor seen in Fig. 1. ($\times 285$.)

points of similarity to what was seen in this patient—a granulomatous response with plasma cells present. In the iododerma, we suspect that the lesions localize to the sebaceous gland areas, representing a reaction to a lipo-iodide antigen presumably escaping from sebaceous glands ruptured by trauma, subsequent to follicular occlusion. In this patient the lesions were strictly localized to the yellow macular xanthomas—the plane xanthoma. None of the lesions were in skin uninvolved by the xanthoma. Equally striking was the fact that the lesions were at sites of known trauma, the belt line, the sites of rubbing on the anterior shoulders, and the wrists. The localization was in keeping with the view that indomethacin (a compound which is insoluble in water but soluble in

fat) had formed an antigen with some lipoidal component of the plane xanthoma (7). This in turn produced the inflammatory immune granulomatous response when released from the cells by trauma. Interestingly, in iododerma the lymphocyte transformation test has been shown to be positive in the presence of iodides (9). We were unable to perform an analogous test to indomethacin in our patient. In this regard, it should be noted that the patch test we performed did not duplicate the patient's exposure or apparent response to indomethacin.

This is the first report linking indomethacin or any drug other than iodides and bromides to the localized reversible inflammatory nodular and tumor lesions. Although indomethacin, 1-(*p*-chlorobenzoyl)-

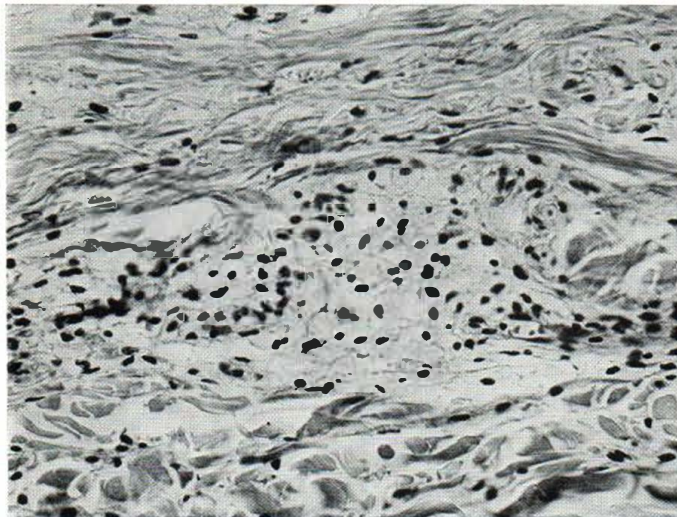


Fig. 3. Fat containing foamy histiocyte clusters in area of plane xanthoma. ($\times 220$.)

5-methoxy-2-methyl iodole-3 acetic acid, has had no secure place in dermatologic therapy (15), other than the recent promise of a topical treatment for sunburn (10), it has received attention as a cause of drug eruptions since it was first introduced ten years ago as a non-steroidal treatment for arthralgias (2). In patients sensitive to aspirin it can induce urticaria (8), or even a fatal asthmatic attack (12). In addition to the usual purpuric and eczematous rashes, it has been reported to be the cause of a widespread bullous drug eruption (3), as well as an urticaria pigmentosa (13).

The presence of an abundance of plasma cells in the skin lesions as well as in the bone marrow raised the possibility of multiple myeloma. The skin changes, however, were not the monomorphic extra-medullary plasmacytoma as have been reported (11), nor did the plasma cells in the skin and marrow show any of the cytologic characteristics of a malignant process. Nonetheless one cannot help wondering whether the outcome would have been multiple myeloma if the indomethacin therapy had been continued indefinitely. Consequently, a search for possible occult antigens would seem indicated in any patient with plane xanthoma and who develops multiple myeloma.

Despite the evidence of the relationship of indomethacin to the emergence and remission of the skin tumefactions, the cause of this patient's plane or macular xanthomatosis of nearly two decades remains completely hidden. The histology suggests that this is a reactive histiocytic process rather than a systemic lipoidosis. The significance and source of the paraproteinemia remains equally obscure. Certainly it did not correlate with the presence of the indomethacin-associated tumors. Nor were we able to demonstrate any anti-lipoprotein antibody activity such as has been recently reported in one case of plane xanthomatosis (4).

ACKNOWLEDGEMENTS

We are grateful to Dr Marvin W. Slatkin for referral of this patient.

This research was supported by the McCabe Fund.

REFERENCES

- Altman, J. & Winkelman, R. K.: Diffuse normolipemic plane xanthoma: Generalized xanthelasma. *Arch Dermatol* 85: 633, 1962.
- Boardman, P. L. & Hart, F. D.: Side effects of indomethacin. *Ann Rheum Dis* 26: 127, 1967.
- Duperrat, B., Puissant, A., Chcrif-Chcikh, J. L., Heintz, C. & Laine, J.-Y.: Toxidermic bulleus (à type de maladie de Dühring-Brocq) provoquées par l'indométacine. *Bull Soc Franc Derm* 76: 26, 1969.
- Kodama, H., Nakagawa, S. & Tanioku, K.: Plane xanthomatosis with antilipoprotein autoantibody. *Arch Dermatol* 105: 722, 1972.
- Krain, L. S.: Cutaneous xanthomatosis and multiple myeloma: Analysis and review. *Cutis* 14: 423, 1974.
- Lai, A. & Fat, R. F. M.: In vitro synthesis of paraproteins in pathological skin. *J Cut Path* 1: 95, 1974.
- Lindskog, G. R., Gustafson, A. & Enerback, L.: Serum lipoprotein deficiency in diffuse "normolipemic" plane xanthoma. *Arch Dermatol* 106: 529, 1972.
- Matthews, J. I. & Stage, D.: Indomethacin, aspirin and urticaria. *Ann Int Med* 80: 771, 1974.
- Nelson, C. T.: Iododerma. *Arch Dermatol* 105: 448, 1972.
- Snyder, D. S. & Eaglstein, W. H.: Topical indomethacin and sunburn. *Br J Dermatol* 90: 91, 1974.
- Stankler, L. & Davidson, J. F.: Multiple extra-medullary plasma-cytomas of the skin. *Br J Dermatol* 90: 217, 1974.
- Timperman, J.: A fatal asthmatic attack following administration of an indomethacin suppository. *J Forensic Med* 18: 30, 1971.
- Vissian, L., Vailland, J.-C. & Manassero, J.: Urticarie pigmentaire apparue au cours d'un traitement par l'indométacine. *Bull Soc Fran Derm* 75: 591, 1968.
- Weber, G. & Pilgrim, M.: Contribution to the knowledge of normolipemic plane xanthomatosis. *Br J Dermatol* 90: 465, 1974.
- Zachariae, H., Niordson, A.-M. & Henningsen, S. J.: Indomethacin in urticaria and histamine induced wealing. *Acta Dermatovener (Stockholm)* 49: 49, 1969.

Received March 17, 1975

W. B. Shelley, M.D.
Department of Dermatology
Hospital of the University of Pennsylvania
Dühring Laboratories Building
3400 Spruce Street
Philadelphia, Pennsylvania 19104
USA