of the term 'suspicious' is defined in cytological practice, the use and interpretation of all the non-definitive phrases among both pathologists and surgeons showed considerable disparity, highlighting the necessity for some limitation, in the use of these and the other definitive terms. Phrases should be mutually understood and acceptable for use by both pathologists and clinicians. To this end, the use of only one of the six definitive phrases in current use is suggested as all semantically convey the same level of certainty. A recommendation for use of a limited repertoire of non-definitive phrases is more difficult to achieve as no single non-definitive term clearly conveys a greater or lesser degree of certainty than any other non-definitive term. National guidelines for the use of phraseological terms in histopathological reporting may be required to address such a problem as there is a clear necessity for non-definitive usage in reports.

In practice, histopathologists are part of a clinical team and regular clinicopathological meetings allow an exchange of information to take place on selected cases. Such meetings also enable the clinician to understand the source of diagnostic difficulties for the pathologist, preventing interpretive ambiguity and facilitating optimal patient management. Off-site private pathology services do not facilitate close contact between pathologists and clinicians and if market forces effect their expansion, the need for unambiguous surgical reports is greater now than ever.

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Tumour related cutaneous elastophagocytosis

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Abstract

Dermal granulomatous inflammation was identified immediately adjacent to seven (77%) of nine atypical fibroxanthomas arising in sun damaged skin. Concomitant elastophagocytosis was observed in five (56%) of these seven patients. Similar inflammation with elastophagocytosis was found in association with only two (6%) of 36 epithelial tumours arising on the same background (10 basal and 10 squamous cell carcinomas, 10 nodular malignant melanomas, and six keratoacinthomas).Granulomatous inflammation is an unusual dermal reaction to tumour and elastophagocytosis is rare. The fact that both of these features occur with inordinate frequency in association with atypical fibroxanthomas, when compared with other, more common skin tumours, suggests that atypical fibroxanthomas might modulate the inflammatory response, either passively, by its dermal location, or actively, by secreting locally effective cytokines.

Keywords: solar elastosis, granulomatous inflammation, elastophagocytosis, skin carcinoma, atypical fibroxanthoma.

Phagocytosis of dermal elastotic material is a well recognised feature of many inflammatory skin disorders and is a defining feature of actinic granuloma. Some investigators believe that the process of elastophagocytosis is a reaction to collagen that has been damaged by ultraviolet light.\(^1\) Others, however, maintain that it is non-specifically associated with local inflammation.\(^2\)

Many skin tumours evoke inflammation and a concurrent granulomatous reaction is thought not to be unusual by some dermatopathologists. Support for this claim, however, appears to be largely anecdotal. Our attention was drawn to this peculiar reaction by the observation of extensive elastophagocytosis adjacent to an atypical fibroxanthoma. This study was undertaken to ascertain the frequency with which elastophagocytosis occurs in association with tumours arising in sun damaged skin and whether or not the type of tumour involved has any bearing on its occurrence.

Methods

Eleven cases of atypical fibroxanthoma were retrieved from archival material stored over a 25 year period. Two of these had arisen in skin that had not been exposed to the sun and therefore were excluded from the study. Similarly, five cases of dermatofibrosarcoma protuberans and 15 dermatofibromas had no evidence of surrounding solar elastosis and were also excluded. However, 10 cases of invasive basal cell carcinoma (BCC), 10 of squamous cell carcinoma (SCC), 10 of nodular malignant melanoma (NMM), and six of keratoacinthomas were included. The nine atypical
composition.

Elastophagocytosis was defined as the presence of clearly discernible fibres within the cytoplasm of non-tumour cells with the characteristics of histiocytes or multinucleate giant cells (MNGC). The fibres stained blue with haematoxylin and cosin, black with elastic–Van Gieson and, in the cases tested, positive for elastin. The number of levels examined in each case ranged from four to 10 (mean, 7).

Results

All of the epithelial tumours exhibited the classic histological features of their type. The atypical fibroxanthomas fulfilled the accepted diagnostic criteria, being pleomorphic cellular tumours situated in the mid to upper dermis and composed of spindle cells, histiocytic cells and bizarre giant tumour cells with frequent mitoses, many of which were atypical (fig 1).

In the atypical fibroxanthomas the epidermis overlying the tumour was invariably ulcerated, but, at the periphery of the tumour in seven of the nine cases, the epidermis was hyperplastic (producing an epidermal “collarette” in four). In one case the hyperplastic epidermis showed diffuse hyperpigmentation of the basal layer.

Atypical fibroxanthoma cells did not react with S100, Mac387, CD34, or keratin antibodies. S100 positive cells, thought to be Langerhans’ histiocytes, were scattered sparsely throughout the atypical fibroxanthomas, as noted previously, and were also present in increased numbers in the adjacent epidermis and, to a lesser extent, in the peripheral inflammatory infiltrate. In this infiltrate histiocytes and, where present, non-tumour giant cells stained positively for Mac387. The vascular network within the atypical fibroxanthomas was delineated by CD34, although, in keeping with the findings of other authors, the tumour cells themselves were negative for either atypical fibroxanthoma cells nor the cells of adjacent intact epidermis, reacted with antibody directed against EGF receptor.

All nine atypical fibroxanthomas had a mild to moderate inflammatory infiltrate at their margins which comprised lymphocytes, histiocytes, plasma cells, and occasional eosinophils. All of the epithelial tumours showed a similar peripheral dermal reaction.

In seven (77%) of the nine cases of atypical fibroxanthoma the inflammatory infiltrate also contained epithelioid histiocytes and MNGC; in five (56%) MNGC could be clearly identified engulfing elastic fibres (fig 2). The nature of the engulfed material was confirmed by staining with elastic–Van Gieson and a positive reaction on immunostaining for elastin. In all five cases with elastophagocytosis the reaction was immediately adjacent to and deep within the tumour, but in one case it also extended well

fibroxanthomas and 36 epithelial neoplasms all arose in skin which showed moderate to severe actinic damage in the form of solar elastosis.

The epithelial tumours were derived from 26 men and 10 women aged from 42 to 85 years (mean age, 74 years). The atypical fibroxanthomas occurred in eight men and one woman aged from 40 to 88 years (mean age, 81 years). All tumours, of both types, arose in the skin of the head, neck, forearm, or hand.

All tissues were fixed in 10% buffered formalin, processed routinely and embedded in paraffin wax. Sections were stained with haematoxylin and cosin, alcin blue at pH 2.5 and by the elastic–Van Gieson method. Selected sections of each atypical fibroxanthoma were stained for S100, Mac387, keratin, CD34 (all from Dako, Glostrup, Denmark), and epidermal growth factor receptor

(EGFr; Triton Diagnostics Inc, Alameda, California, USA) using the Streptavidin-biotin method. Using the same technique, sections from three of the atypical fibroxanthomas were immunostained for elastin (Sigma, St Louis, Missouri, USA).

Figure 1 Representative area of an atypical fibroxanthoma showing the characteristic composition of the tumour with spindle cells, histiocytic cells and bizarre giant cells. An abnormal mitosis is also visible (centre right).

Figure 2 A focus of granulomatous inflammation lying beneath an atypical fibroxanthoma. Scattered giant cells are present, one of which (centre) can be seen engulfing a sinuous elastic fibre.
Tumour related cutaneous elastophagocytosis

be beyond the lateral margin of the atypical fibroxanthoma. Even where elastophagocytosis could not be identified on several levels, the granulomatous inflammation was closely associated with the elastotic material. Sarcoid-like granulomata, asteroid bodies or palisade histiocytes were not identified, nor was there any evidence of necrobiosis. Alcianophilic material was present in xanthoma-like tumour cells in three of the nine cases of atypical fibroxanthoma, but neither mucin pooling nor granuloma associated mucin was evident.

Five of the 36 epithelial tumours (two BCC, two keratoacanthomas and one NMM) demonstrated a peripheral MNGC reaction. Of these, the granulomatous reaction in these three was clearly directed against either the contents of ruptured, entrapped skin appendages (one NMM and one BCC) or necrotic tumour keratinocytes (one keratoacanthoma). The remaining two tumours (one BCC and one keratoacanthoma) were associated with small areas of granulomatous inflammation in which elastophagocytosis was evident, giving an incidence of 10% and 16% in BCC and keratoacanthoma, respectively. Therefore, the overall incidence of this phenomenon in the 36 epithelial tumours was 6%.

Discussion

Chronic exposure of the skin to ultraviolet light results in the appearance of increased amounts of fibrillar material in the dermis which has the staining characteristics and chemical composition of elastin. Whether this material is the end product of collagen degradation or neof ormation of elastin by ultraviolet stimulated fibroblasts remains controversial. In xerotic granuloma there is a localised inflammatory reaction in which MNGC phagocyte and clear this elastotic material. This suggests that this phenomenon is not a specific reaction to normal elastin, as has been proposed, because the elastophagocytosis is focal whereas the elastosis is widespread. It seems more likely that some other factor, perhaps local trauma, is responsible for initiating an inflammatory response and that histiocyte recruitment, giant cell formation and elastophagocytosis are a cascade of secondary events.

Neoplasms of the skin commonly excite a local inflammatory reaction and, as most epithelial tumours arise in areas that have been exposed to ultraviolet light, one would expect that elastophagocytosis would be observed regularly in this situation if the above hypothesis was true. In this study, however, few epithelial tumours evoked this particular type of reaction, whereas it was evident in association with most of the atypical fibroxanthomas. Kempson and McGavran recorded the phagocytosis of unspecified material in their cases of atypical fibroxanthoma, but the process was not illustrated and it is implicit in the text that the authors were referring to the phagocytic activity of tumour cells.

Given that the cases presented here were roughly equivalent for age, sex and site, other variables that might influence the type of inflammatory reaction were considered. These included the dermal or epidermal location of the tumour, its growth rate and its possible synthetic activity.

We were unable to test the first postulate because the five available cases of dermatofibrosarcoma protuberans and the 15 dermatofibromas all arose in skin with no evidence of actinic damage.

The second possibility, that growth rate might influence the incidence of elastophagocytosis, is unlikely as in the fast growing tumours—that is, NMM and keratoacanthoma, the incidence of elastophagocytosis did not differ significantly from that observed for BCC and SCC, both slow growing tumours. Elastophagocytosis was associated with atypical fibroxanthoma more frequently than with either the fast or the slow growing epithelial tumours.

The third hypothesis is more plausible. Tumour-like lesions of the dermis, such as dermatofibromas, are composed of histiocytes, fibroblasts and myofibroblasts in proportions similar to those seen in atypical fibroxanthomas. Epidermal hyperplasia is frequently associated with dermatofibroma and some authors have suggested that this phenomenon is ‘... a reaction to influences from the underlying fibrohistiocytic abnormality ...’ or is due to ‘... stimulation by growth factors released by the dermal lesion...’. An analogous mechanism might reasonably be invoked for the epidermal hyperplasia associated with atypical fibroxanthomas. The nature of these influences or factors, however, remains obscure. It is evident from this study that epidermal hyperplasia in atypical fibroxanthomas is not mediated by upregulation of EGF in keratinocytes, as visualised using immunohistochemistry.

If it is accepted that atypical fibroxanthoma, like dermatofibroma, exerts a trophic influence on the epidermis, it is reasonable to suggest that it might also affect adjacent cells. We speculate that a product of the atypical fibroxanthoma is responsible for modulating the nonspecific inflammatory reaction, thereby inducing elastophagocytosis.

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