Virchows Archiv A Pathol Anat (1992) 420:113–115

Virchows Archiv A
Pathological Anatomy and Histopathology

Editorial

The significance of inflammation and regression in melanoma

M.G. Cook

Department of Histopathology, Royal Surrey County Hospital, Guildford, Surrey GU2 5XX, UK

Received December 3, 1991 / Accepted January 10, 1992

A lymphohistiocytic infiltrate in melanocytic lesions is relevant to both diagnosis and prognosis but in a highly complex way not yet clearly understood. Some benign melanocytic naevi may have an associated lymphocytic infiltrate, seen particularly intensely in the halo phenomenon, but more often the presence of a mononuclear cell infiltrate is a sign of an increasing degree of atypia, usually presumed to represent progression towards malignancy. An inflammatory infiltrate is an important diagnostic feature of the putative precursor lesions melanocytic dysplasia and lentigo maligna, and as such it is considered to represent part of the host response to developing neoplasia.

T-lymphocytes and macrophages are the predominant cells in the inflammatory infiltrate (Bröcker et al. 1990). These may be attracted by a change in the tumour-associated antigens (Johnson et al. 1990). Whether melanoma progression occurs in spite of or because of the inflammatory response is not clear, but there is a change in the subtypes of T-cells from a predominant helper T4 subtype in early lesions to cytotoxic T8 lymphocyte predominance in thicker lesions (Bröcker et al. 1990; Simony et al. 1991). Bröcker et al. (1990) also showed an increase in mature macrophages (subtype 25 F9) in more aggressive melanomas. On the other hand, regression was associated with inflammatory macrophages (subtype 27 E10) and CD 4 T-lymphocytes (Tefany et al. 1991).

The significance of the inflammatory infiltrate in melanoma appears to vary, not only according to the cell type, but also according to its distribution within a lesion. The associated stromal reactions, amounting to regression, may also have prognostic importance, but the literature is contradictory on this point. Some authors argue that a lymphocytic infiltrate around a melanoma is associated with a good prognosis (Day et al. 1982; Drzewiecki and Anderson 1982; Schmoeckel et al. 1983; Kopf et al. 1987), but the presence of plasma cells in the infiltrate is alleged to reverse the effect (Kopf et al. 1987; Mascaro et al. 1987). The good prognostic effect is presumed to work through inhibitory lymphocyte growth factors secreted by suppressor/cytoxic CD8 cells (Kornstein et al. 1983), whereas the adverse effect of plasma cells might be mediated by the production of "blocking" antibodies inhibiting the otherwise favourable cytotoxic immunological response.

Regression may be considered as an extension of the inflammatory response resulting in destruction of tumour cells with their eventual replacement by fibrosis. As such it might have been expected that it would have a favourable effect on prognosis. However, roughly equal numbers of diametrically opposed views on the prognostic significance of regression have been published. Some (Gromet et al. 1978; Yonemoto and Paladugu 1983; Naruns et al. 1986; Slingluff et al. 1988; Blessing et al. 1990) suggest that the presence of regression in thin lesions, most often defined as thinner than 0.76 mm, is associated with a higher rate of recurrence and shorter survival. Others (McGovern et al. 1983; Trau et al. 1983; Cooper et al. 1985; Wanebo et al. 1985) suggest it is not associated with a higher rate of recurrence. Furthermore, one group of workers (Gromet et al. 1978) when analysing the same patient group after a longer period of follow up (Kelly et al. 1985) reported that the initial high incidence of recurrence in thin regressed lesions was later matched by the incidence of metastases in the non-regressed thin lesions, so that there was no long-term difference in survival in the two groups.

Other studies have made more qualified comments on the effects of regression. Ronan et al. (1987) suggested that extensive (greater than 77%) regression is associated with aggressive metastasising melanomas and that those lesions with less than 77% regression only rarely metastasize. Cooper et al. (1985), whilst reporting no overall bad prognostic effect of regression, did concede extensive scarring in melanoma may be a bad sign. Clark et al. (1989) made similar observations about regression in radial growth phase melanomas, but also noted that regression in vertical growth phase is associated with shorter survival. Sondergaard and Schou (1985) also reported a variable significance of regression de-

pending on the thickness of the affected melanoma. In thin lesions (less than 1 mm), they noted that regression unfavourably influenced outcome, but in thick lesions (more than 2 mm) prognosis was improved.

Shaw et al. (1989) reported no difference in the incidence of regression in subsequently metastasizing compared with non-metastasizing stage 1 "thin" lesions, but they did note the invariable presence of regression in stage II thin lesions. They argued that the presence of lymph node metastases induces a change leading to regression in the primary lesion. Trau et al. (1983) ascribed the higher rate of metastasis in thin regressed lesions compared with non-regressed melanomas to the lack of thorough step-sectioning of the tumours. They argued that deeper invasion would be revealed in most regressed lesions, taking them out of the "thin" category and explaining their greater propensity for metastasis.

Other reasons for these wide discrepancies in interpretation on the significance of regression are not obvious, but are likely to be related to the different definitions of regression used by the various authors. This is suggested by the variation of the reported incidence of regression from 20% (Kelly et al. 1985) to 58% (Gromet et al. 1978) in different centres. The more recent trend seems to be to restrict the term regression to an established form, that is one in which the lesions show extensive loss of melanoma cells with segmental replacement by fibrosis. There is a reasonable concurrence that the presence of extensive scarring regression is a bad prognostic sign in terms of incidence of lymph node metastases. However, Sagebiel (1985) has argued that regression does not confer a likelihood of shorter survival, although there may be a higher incidence of lymph node metastases in the short term. This would imply that there is an essential difference in the biological characteristics of some melanomas. It may be that those melanomas, which are associated with chronicity of the primary cutaneous lesions, show regression and a predisposition to metastasize to lymph nodes, have little tendency to systemic metastasis (Naruns et al. 1986), so that long-term survival is no worse or even better than a comparable melanoma not showing regression.

The paradox of an antitumour cytotoxic lymphocytic infiltrate being associated with an apparently worse prognosis has been explained by the features of regression disguising a previously thicker lesion which has already metastasized. This is not supported by the clinical observation that regression is confined to lesions with a predominant flat growth pattern and histologically the vertical growth phase characteristically does not exhibit regression (Kelly et al. 1985). Nevertheless the probability remains that the metastases in regressed lesions are derived from a thin vertical growth phase obscured by the regressive process. It is possible that regression, by causing destruction of the non-aggressive component of a melanoma, confers a growth advantage on a small component of the lesion which whould otherwise have marginal metastasizing ability. The regressive process invariably has a component of vascular proliferation providing a route of spread, but the overall aggressive potential of this type of melanoma appears limited when its spread is confined to lymph nodes. The interaction of lymph node and metastatic melanoma cells produces an exaggeration of or initiates the process of regression in the primary. Melanomas which metastasize systemically may not show any features of regression in the cutaneous primary (Naruns et al. 1986) and this group of tumours invariably shows shorter survival.

Melanomas which have a prominent vertical growth phase do show some variation in survival even when comparing like thickness. One of the features which may influence this aggressive potential is the inflammatory response. This should be distinguished from the process of the regression which is less frequently seen in the vertical growth phase. The inflammatory infiltrate in this phase has no fibrotic or vascular component and consists of tumour infiltrating lymphocytes (TIL). A band of lymphocytes at the deep margin of the tumour has already been reported to be associated with better prognosis (Kopf et al. 1987), but this pattern of peripheral lymphocytic reactions is not accepted as a "tumour infiltrating lymphocytic" response by Clark et al. (1989). Their work has shown that the rate of survival at 8 years in vertical growth phase melanomas is improved when there are TIL. The response is "dose related" in that melanocytes should be separated and at least partially surrounded by lymphocytes throughout the vertical growth phase or across the whole of its deepest part for the reaction to be termed "brisk". A focal or scattered infiltrate is classified "non-brisk" and any other pattern including a peripheral lymphocytic infiltrate is classed as "absent". The survival is best in those patients showing a "brisk" TIL reaction and worst when it is "absent".

To form a coherent hypothesis based upon the divergent reports of the prognostic significance of inflammation and regression is difficult. It is essential to consider regression as a different process from TIL and it also seems important to consider horizontal growth phase, both in situ and invasive, separately from vertical growth phase.

Horizontal growth phase does not have metastatic potential, is characteristically associated with a prominent lymphocytic infiltrate and frequently shows areas of regression. Since these melanomas do not metastasize the presence of either inflammation or regression cannot affect survival. However, horizontal growth phase is not synonymous with a "thin" lesion. Some thin melanomas do metastasize and extensive regression in these thin lesions appears to be associated with a higher incidence of lymph node metastases in the short term, although it is questioned whether there is any effect on long-term survival (Sagebiel 1985). Theoretically the thin melanoma must have harboured a vertical growth phase component, which was not recognised either because of its small size, lack of serial sectioning or because it had been disrupted or destroyed by the regressive process.

In the recognisable vertical growth phase melanoma, survival is unfavourably influenced by a high mitotic count and greater Breslow thickness, but favourably by the presence of TIL, presumably of cytotoxic (T_8) type. The presence of regression which must include segmental

fibrous replacement of a melanoma, with or without a T_4 type lymphocytic reaction (Tefany et al. 1991), appears to have a detrimental effect on survival. Whether the regression in vertical growth phase is masking the thickness of the tumour or provoking a more aggressive behaviour is not yet determined.

The hypothesis appears to reconcile most of the published reports concerning lymphocytic infiltrate and regression in melanoma, but much work remains to be carried out to clarify the biological processes involved. Furthermore, the considerable diversity of behaviour of melanoma is only partially explained by the complexity of the host response. The recognition of likely aggressive behaviour in any melanoma whether by immunological, molecular biological or histological means, remains to a large extent an enigma.

References

Blessing K, McLaren KM, McLean A, Davidson P (1990) Thin malignant melanomas (less than 1.5 mm) with metastasis: a histological study and survival analysis. Histopathology 17:389–395

Bröcker E-B, Macher E, Sorg C (1990) Changes in the tumour-associated inflammatory infiltrates in the course of local and systemic progression of cutaneous melanoma. In: Ferrone S (ed) Human melanoma. Springer, Berlin Heidelberg New York, pp 278–293

Clark WH, Elder DE, Dupont G, Braitman LE, Trock BJ, Schultz D, Synnestvedt M, Halpern AC (1989) Model predicting survival in Stage 1 melanoma based on tumour progression. J Natl Cancer Inst 81:1893–1904

Cooper PH, Wanebo HJ, Ward Hagar R (1985) Regression in thin malignant melanoma. Arch Dermatol 121:1127–1131

Day CL, Mihm MC, Lew RA, et al. (1982) Prognostic factors for patients with clinical stage 1 melanoma of intermediate thickness (1.51–3.99 mm). Ann Surg 195:35–43

Drzewiecki KT, Andersen PK (1982) Survival with malignant melanoma. A regression analysis of prognostic factors. Cancer 49:2414–2419

Gromet MA, Epstein WL, Blois MS (1978) The regressing thin malignant melanoma. A distinctive lesion with metastatic potential. Cancer 42:2282–2292

Johnson JP, Stade BG, Rothbächer U, Lehmann JM, Riethmüller G (1990) Melanoma antigens and their association with malignant transformation and tumour progression. In: Ferrone S (ed) Human melanoma. Springer, Berlin Heidelberg New York, pp 106–118

Kelly JW, Sagebiel RW, Blois MS (1985) Regression in malignant melanoma. A histologic feature without independent prognostic significance. Cancer 56:2287–2291

Kopf AW, Welkovich B, Frankel RE, Stoppelmann EJ, Bart RS, Rogers GS, Rigel DS, Friedman RJ, Levenstein MJ, Gumport SL, Henessey P (1987) Thickness of malignant melanoma: global analysis of related factors. J Dermatol Surg Oncol 13:345–420

Kornstein MJ, Brooks JSJ, Elder DE (1983) Immunoperoxidase localisation of lymphocyte subsets in the host response to melanoma and naevi. Cancer Res 43:2749–2753

Mascaro JM, Molgo M, Castel T, Castro J (1987) Plasma cells within the infiltrate of primary cutaneous malignant melanoma of the skin. Am J Dermatopathol 9:497–499

McGovern VJ, Shaw HM, Milton GW (1983) Prognosis in patients with thin malignant melanoma: influence of regression. Histopathology 7:673–680

Naruns PL, Nizze A, Cochran AJ, Lee MB, Morton DL (1986) Recurrence potential of thin primary melanomas. Cancer 57:545–548

Ronan SG, Eng AM, Briele HA, Shioura NN, Das Gupta TK (1987) Thin malignant melanomas with regression and metastases. Arch Dermatol 123:1326–1330

Sagebiel R (1985) Regression and other factors of prognostic interest in malignant melanoma (editorial). Arch Dermatol 121:1125–1126

Schmoeckel C, Bockelbrink A, Bockelbrink H, Braun-Falco O (1983) Low and high risk malignant melanoma. II. Multivariate analyses for a prognostic classification. Eur J Cancer Clin Oncol 19:237–243

Shaw HM, McCarthy SW, McCarthy WH, Thompson JF, Milton GW (1989) Thin regressing malignant melanoma: significance of concurrent regional lymph node metastases. Histopathology 15:257–265

Simony J, Rossi JF, Shishehian B, Ursule E, Radal M, Pujol H (1991) Characterization of proliferative cells in malignant melanomas and their inflammatory infiltrates. Cancer Detect Prevent 15 3:183–187

Slingluff CL, Vollmer RT, Reintgen DS, Seigler HF (1988) Lethal "thin" malignant melanoma. Identifying patients at risk. Ann Surg 208 2:150–161

Sondergaard K, Schou G (1985) Survival with primary cutaneous malignant melanoma, evaluated from 2012 cases. Virchows Arch [A] 406:179–195

Tefany FJ, Barnetson RStC, Halliday GM, McCarthy SW, McCarthy WH (1991) Immunocytochemical analysis of the cellular infiltrate in primary regressing and non-regressing malignant melanoma. J Invest Dermatol 97:197–202

Trau H, Rigel DS, Harris MN, Kopf AW, Friedman RJ, Gumport SL, Bart RS, Robson W, Grier N (1983) Metastases of thin melanomas. Cancer 51:553–556

Wanebo HJ, Cooper PH, Ward Hagar R (1985) Thin (less than 1 mm) melanomas of the extremities are biologically favourable lesions not influenced by regression. Ann Surg 201 4:499–504

Yonemoto RH, Paladugu RR (1983) Biologic behaviour of thin malignant melanomas with regressive changes. Arch Surg 118:41–44