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Blood Group Antigens in Vascular Tumours

Evaluation of the Immunoperoxidase Technique

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Summary. Determination of blood group isoantigens A, B and H, was performed in benign and malignant vascular tumours of the skin and subcutaneous tissue, using the immunoperoxidase technique. No differences were noted between benign haemagioendotheliomas from children or adults: neither tumour showed the presence of antigens in intercapillary cells. Reactive conditions such as angiolymphoid hyperplasia with eosinophilia showed an intense positive reaction to blood group substances of the endothelial proliferative cells. In malignant tumours no relationship between tumour differentiation and loss of blood group isoantigens was seen. Cases of Kaposi's sarcoma did not show antigens in spindle cells or capillaries but in medium sized vessels variable preservation or loss of blood group isoantigens was found.

Key words: Blood group antigens – Vascular tumours – Immunoperoxidase technique.

Introduction

A number of reports of loss of the epithelial expression of blood group antigens (BGA) associated with the development of carcinomas at various sites have been made (Davidsohn and Ni 1969; Davidsohn et al. 1969; Davidsohn et al. 1971 a; Davidsohn et al. 1971 b). These observations were amplified by Stejskal et al. (1978) and Weinstein et al. (1979) and apart from the earlier report of preservation of BGA in gastric carcinoma by Eklund et al. (1963) a consensus view of this phenomenon seems to have emerged. A direct relationship between the degree of differentiation of the tumour and the loss of BGA was also described by certain authors (Davidsohn 1972; Bergman and Javadpour 1978).

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Others have failed to find such an association (Denk et al. 1974; Slocombe et al. 1980) and have described a change of expression of BGA in tumour cells (Häkkinen 1970; Slocombe et al. 1980).

We wished to extend our observations on epithelial tumours to those of blood vessels. BGA's are present in endothelial cells (Glynn and Holborow 1959; Holborow et al. 1960; Szulman 1960) and have been studied in vascular tumours by Feigl et al. (1976) using a haemagglutination technique. We report here the results of a study on a number of vascular tumours from the skin and subcutaneous tissues, using the more sensitive immunoperoxidase method and compare our results with those of Feigl et al. (1976).

Material and Methods

The number of cases examined, the type of tumours and the expected blood group antigen which would be present are listed in Table 1. The method by which specific antisera to human blood group substances were obtained and the immunoperoxidase technique used, an adaptation of that performed by Kovacs et al. (1976) have been recently described by Slocombe et al. (1980). All sections were cut from paraffin embedded blocks of formalin fixed tissue, using archive material. They were examined for the presence of A, B and H blood group substances. Endothelial cells lining the lumina of normal vessels, blood plasma, epithelial cells of the epidermis and sweat glands which normally contain BGA, served as positive controls. Pericytes, smooth muscle cells and connective tissue normally lack the antigens.

Table 1. Cases, types of tumours, blood group substances of the patients and behaviour of BGA in neoplastic cells

Pathological diagnosis	No. of cases	Expected BGA			Loss of BGA in neoplastic cells
		H	A	B	
Cavernous haemangioma	5	5	–	–	–
Capillary haemangioma	4	2	1	1	–[a]
Lymphangioma	3	1	1	1	–
Glomus tumour	4	3	1	–	All cases
Haemangiopericytoma	3	2	–	1	All cases
Benign haemangio-endothelioma[c]	12	8	3	1	In intercapillary cells
Angiolymphoid hyperplasia with eosinophilia	3	2	1	–	–
Angiosarcoma	6	4	2	–	5
Lymphangiosarcoma	2	2	–	–	Both cases[b]
Kaposi's sarcoma	8	5	2	1	?

[a] Partial loss of BGA in neoplastic cells in solid clumps
[b] Preservation of BGA in associated squamous carcinoma
[c] Three of the cases occurring in adults

Results

A summary of the results appears in Table 1.

Benign Tumours

Cavernous haemangiomas showed BGA exclusively on the endothelial cells lining the large sinus-like spaces (Fig. 1a). In capillary haemangiomas BGA were located on the surface of the endothelium of small and medium sized capillaries (Fig. 1b). Endothelial cells arranged on the periphery of vessels and in solid clumps only occasionally showed BGA (Fig. 1c).

Endothelial cells covering the lumen of lymphatics in lymphangiomas were positive for BGA. Glomus tumours and haemangiopericytomas presented the same characteristic pattern of staining: BGA was confined to the endothelial cells, while cells surrounding the capillaries failed to show positive staining.

Twelve cases of a more cellular variant of capillary haemangioma (variously designated as "strawberry naevus", hypertrophic haemangioma, compact haemangioma, angioblastic haemangioma and benign haemangioendothelioma) (Fig. 2a) were examined: three from adults and the rest from children (1 month to 6 years of age). In both adult and juvenile types BGA was weakly present in the endothelial cells lining small capillaries, while none of the cases showed BGA in the intercapillary cells (Fig. 2b).

In order to make comparisons between reactive conditions and neoplastic processes three cases of angiolymphoid hyperplasia with eosinophilia (Fig. 3a) were examined. All three cases showed an intense positive reaction for BGA in the proliferating endothelial cells (Fig. 3b).

Malignant Tumors

Neoplastic cells were BGA negative in all but one case of angiosarcoma. This tumour was composed of irregular vascular spaces lined by more than two layers of anaplastic cells, often multinucleated. These cells showed a very strong reaction to BGA, in many fields (Fig. 4a). In contrast another angiosarcoma which was apparently better differentiated being formed of large vessels covered by one layer of cells, showing only moderate atypia, did not show BGA on endothelial cells (Fig. 4b).

Two cases of lymphangiosarcoma (Fig. 5a) were examined. Neither showed BGA on tumour cells (Fig. 5b), nevertheless, one of these, which was located on the leg of a 77 year old male, was associated with a well differentiated squamous carcinoma which showed a clear reaction to BGA on the neoplastic cells (Fig. 5c).

In Kaposi's sarcoma the majority of medium or large tumour vessels did not show BGA (Fig. 6a), however, in some areas some medium sized vessels were covered by an apparently abnormal endothelium which showed BGA reactivity; capillary channels and spindle cells showed no BGA reactivity (Fig. 6b).

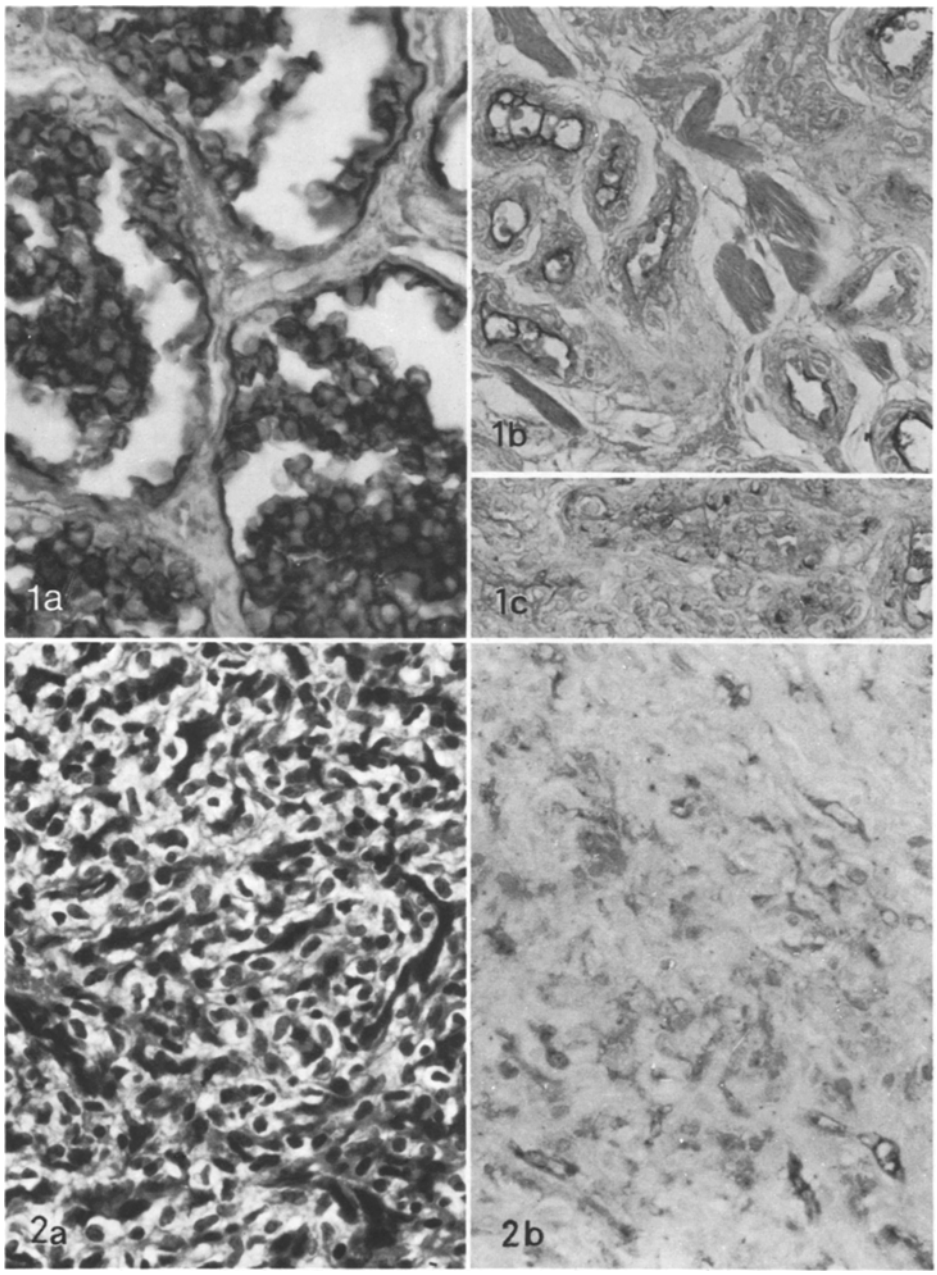


Fig. 1. a Cavernous haemangioma showing BGA positive endothelial cells. Connective tissue negative. Immunoperoxidase stain with anti-H. ×400. **b** Capillary haemangioma. Specific staining of endothelial cells located in the lumen of capillaries. Immunoperoxidase stain with anti-A. ×250. **c** Same case as Fig. 1b. Occasionally, positive endothelial cells located on the periphery of the capillaries and in solid areas are observed. Immunoperoxidase stain with anti-A. ×250

Fig. 2. a Capillary haemangioma with a higher degree of cellularity (benign haemangioendothelioma) formed by polymorphic cells showing little tendency to blood-vessel formation. H & E ×250. **b** Same case as Fig. 2a. Endothelial cells of small capillaries are positive, whereas intercapillary cells do not show BGA. Immunoperoxidase stain with anti-H. ×250

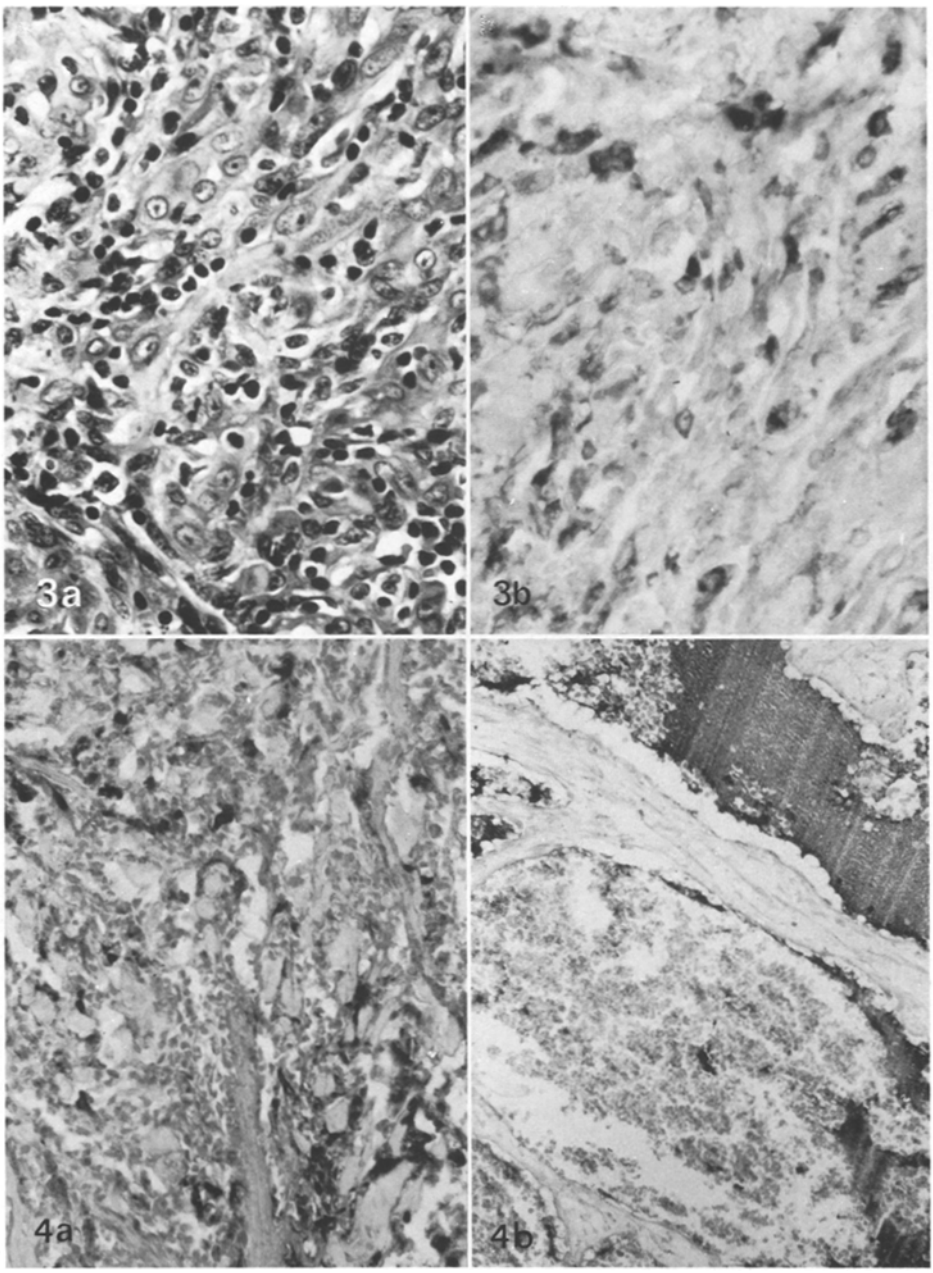
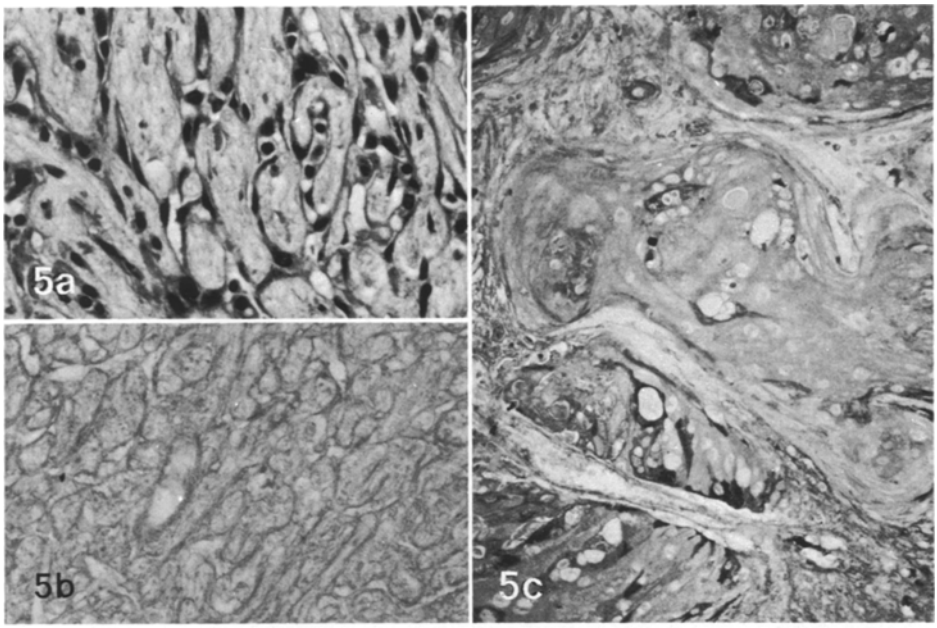


Fig. 3. a Angiolymphoid hyperplasia with eosinophilia. A group of proliferating vessels composed of swollen endothelial cells surrounded by inflammatory infiltrate. H & E ×250. **b** Same case as Fig. 3a. Strong positive staining of proliferating endothelial cells. Immunoperoxidase stain with anti-A. ×250

Fig. 4. a Anaplastic angiosarcoma showing strong positive staining in some tumour cells. Immunoperoxidase stain with anti-H. ×250. **b** Angiosarcoma composed of large sinus-like spaces covered by one layer of neoplastic cells. Note loss of BGA on endothelial tumour cells, while plasma is strongly positive. Immunoperoxidase stain with anti-A. ×100



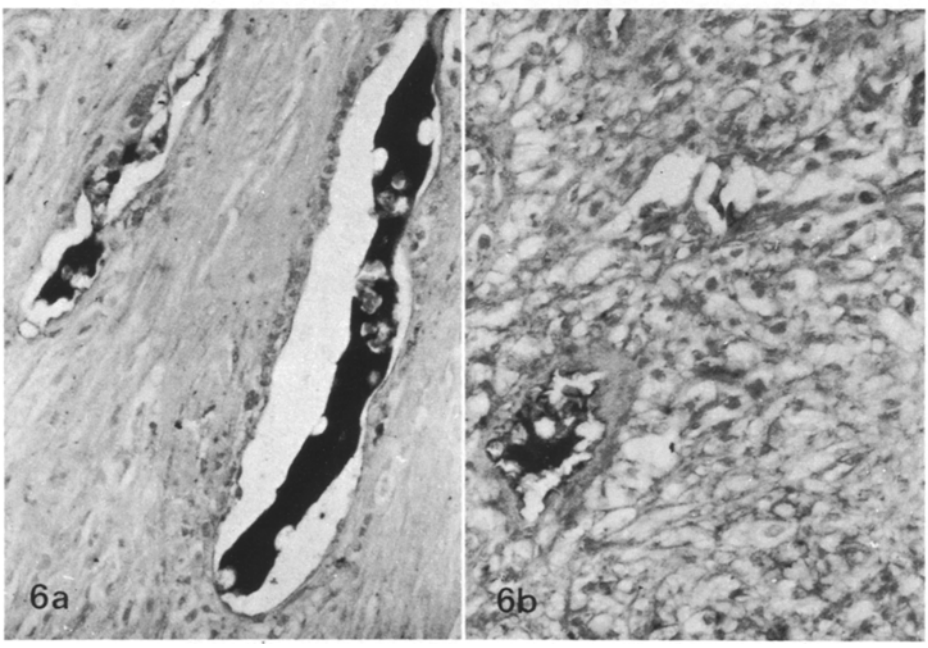


Fig. 5. a Lymphangiosarcoma showing intercommunicating vascular channels covered by bizarre endothelial cells. H & E ×250.
b Same case as Fig. 5a. Loss of BGA on endothelial cells lining vascular slits. Immunoperoxidase stain with anti-H. ×250.
c Same case. An associated well differentiated squamous carcinoma shows preservation of BGA on neoplastic cells. Immunoperoxidase stain with anti-H. ×100

Fig. 6. a Medium sized and large vessels show loss of BGA in Kaposi's sarcoma. Note strong positive staining of the plasma. Immunoperoxidase stain with anti-B. ×250.
b Spindle cells and capillaries show loss of BGA. Occasionally, some medium sized vessels show presence of BGA on endothelial cells. Immunoperoxidase stain with anti-H. ×250

Discussion

Like Feigl et al. (1976) we found that only the endothelial cells of cavernous and capillary haemangioma stained with BGA – we assume that "the cells located in the centre of solid buds" which they describe are endothelial. Unlike them we found positive staining in the endothelial cells in these proliferating tufts to be patchy. There was staining of endothelial cells only in glomus tumours and haemangiopericytomata, and in lymphangiomata as Feigl and his colleagues reported. In benign haemangioendothelioma we found positive reaction in endothelial cells in both children and adults although intercapillary cells were BGA-negative.

The uniform pattern of positive reaction of the cases of angiolymphoid hyperplasia with eosinophilia which were examined leads us to the conclusion that the vascular proliferation is of endothelial origin, although an origin from a transitional endothelial-histiocytic cell has been postulated (Castro and Winkelmann 1974). Clearly, whether or not the condition is reactive or neoplastic cannot be decided by use of this immunoperoxidase technique. The observations in angiosarcoma and lymphangiosarcoma show a considerable variation which is not surprising in view of the heterogeneity of all types of malignant tumours. No correlation between tumour differentiation and preservation of BGA could be demonstrated as pointed out by Denk et al. (1974) and Slocombe et al. (1980) for gastric carcinomas. In our series, a well differentiated angiosarcoma showed loss of BGA, whereas a very anaplastic tumour of the same type showed preservation of antigen. Unlike us, Feigl et al. (1976) observed preservation of BGA in only one case of well differentiated angiosarcoma. However, in our case of lymphangiosarcoma associated with squamous carcinoma differences in the expression of BGA in the two lesions might be related to a possible relationship between their degree of differentiation. The presence of some vessels with BGA-positive cells in cases of Kaposi's sarcoma supports the partial histogenesis of this tumour from primitive endothelial cells (Rosai et al. 1976), although we cannot exclude the possibility that these BGA positive endothelial cells are reactive: they showed no truly neoplastic features.

Immunoperoxidase techniques are a sensitive method of demonstrating blood group antigens. In benign vascular tumours BGA can be demonstrated consistently in endothelial cells but their appearance in malignant lesions, as in carcinomas, is variable. We saw no example of altered blood group expression, i.e. change from B to H expression as we have found in some gastric tumours (Slocombe et al. 1980). It is likely that staining with these reagents may be helpful in occasional cases of tumours of obscure origin, in identifying cells of endothelial type but positive reactions cannot be expected in all malignant vascular tumours. The use of the method is, in our view, not helpful in the classification of vascular lesions in the way which Feigl and his colleagues suggest, simply because of the variability of expression of this aspect of the phenotype in neoplastic lesions.

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