Virchows Arch (1996) 428:301–304

CASE REPORT

Masaharu Fukunaga · Yasuhiko Endo
Fumiaki Masui · Takashi Yoshikawa · Eisei Ishikawa
Shinichiro Ushigome

Retiform haemangioendothelioma

Received: 5 January 1996 / Accepted: 12 February 1996

Abstract A case of retiform haemangioendothelioma (RH), a recently described rare cutaneous low-grade angiosarcoma, is presented. A 75-year-old female had a 3.5 cm cutaneous nodule in her right lower thigh with 10 year preoperative duration. Microscopically, the dermis and subcutis contained a diffuse and infiltrative neoplasm which was characterized by long arborizing blood vessels arranged in a retiform pattern lined by cuboidal and flattened cells, occasional hobnail appearance of endothelial cells, and a prominent small lymphocytic infiltrate. Small solid areas were also found. Neither significant cellular atypia nor mitotic activity was observed. Immunohistochemically, the tumour cells reacted with endothelial markers (CD31, CD34, factor-VIII-related antigen) and bound *Ulex europaeus* agglutinin 1. There was no pericytic component within the tumour. The tumour was diploid by flow cytometry. The patient had a local recurrence 27 months after the excision. These findings support the view that RH is a low-grade angiosarcoma and indicate that RH must be distinguished from conventional angiosarcoma.

Key words Hemangioendothelioma · Retiform · Angiosarcoma · Dabska tumour · Vascular tumour

Introduction

The term "haemangioendothelioma" is used to refer to vascular tumours that have a biological course intermediate between a haemangioma and conventional angiosarcoma [11]. Retiform haemangioendothelioma (RH) is a very rare, but distinctive vascular tumour recently described by Calonje et al. [1]. RH has an indolent clinical course and is considered to be a low-grade angiosarcoma occurring in the skin or subcutaneous tissue of mainly young adults. To the best of our knowledge, there has been no reported RH since Calonje et al. [1] described their series of 15 cases. We describe a case of RH in a 75-year-old female.

M. Fukunaga (✉) · Y. Endo · F. Masui · T. Yoshikawa
S. Ushigome
Department of Pathology, Jikei University School of Medicine, 3-25-8, Nishi-shinbashi, Minato-ku, Tokyo, 105 Japan
Tel.: (81) 3-3433-1111, ext. 2231, Fax: (81) 3-3435-1922

E. Ishikawa
Mitusi Memorial Laboratory, Jikei University School of Medicine, Tokyo, Japan

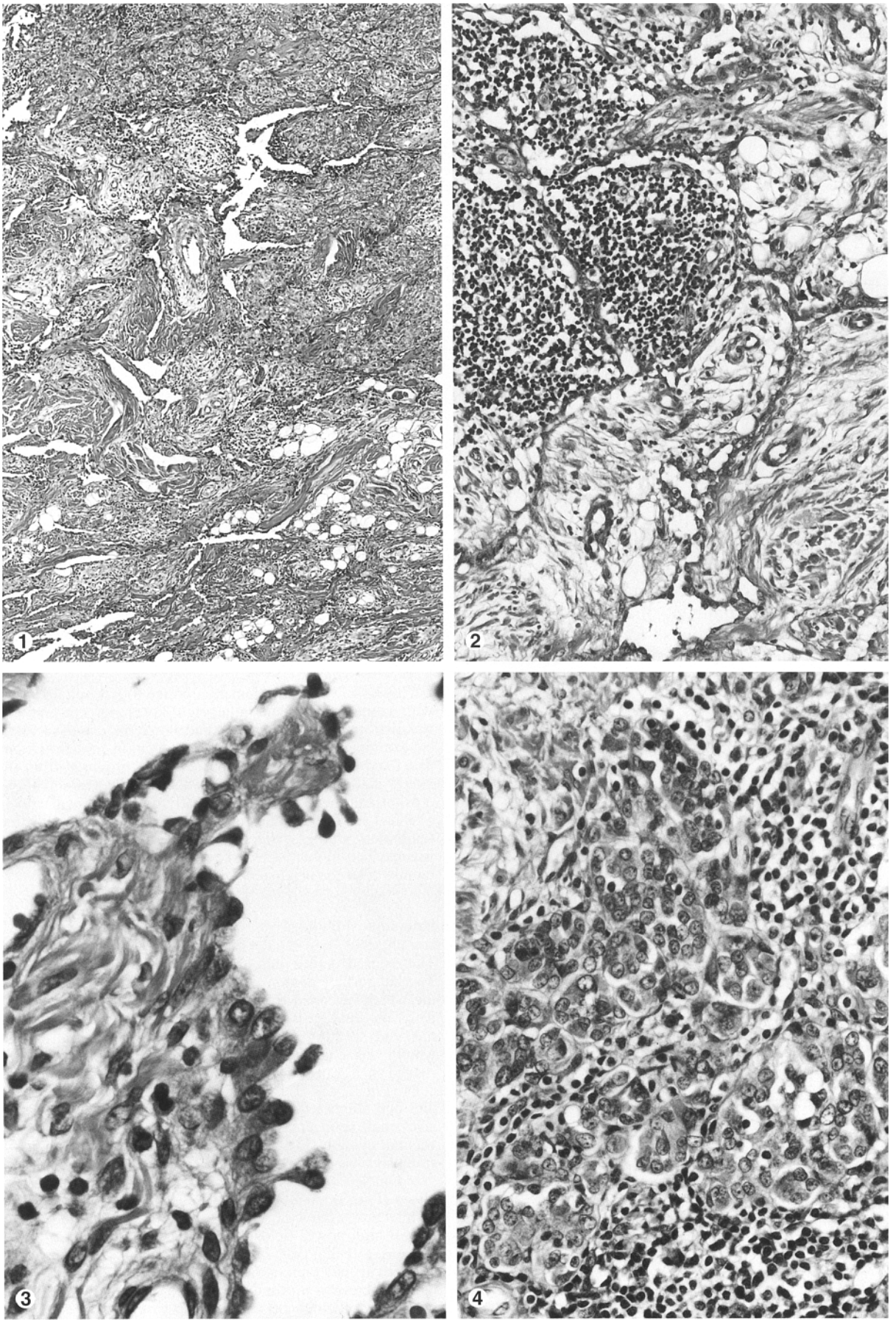
Case report

Clinical history

A 75-year-old Japanese female reported to a hospital in June 1993 with a cutaneous nodule in her right lower leg. The nodule, which was first noticed 10 years ago, had slowly increased in size. Physical examination revealed a 3.5 cm×2.5 cm in size, firm, nontender, and fixed brownish nodule located 5 cm proximal from the right lateral malleolus. The surface of the nodule was smooth without erosion and the lesion was clinically diagnosed as haemangioma. She had no history of irradiation or lymphoedema in that area. Laboratory studies yielded normal results. The cutaneous nodule was excised in June 1993. The patient had a local recurrence 27 months after the original excision.

Pathological findings

The excised nodule measured 3.5×2.3×2.0 cm and was rubbery. The cut-surface demonstrated an ill-defined brownish white nodule which extended from the dermis to the subcutis. Microscopically, the epidermis showed no significant abnormality. The dermis and subcutis contained a diffuse and infiltrative neoplasm which was characterized by long arborizing blood vessels arranged in a retiform pattern and lined by cuboidal and flattened cells (Figs. 1–3). These vessels extended between collagen bundles and adipose tissues in the same fashion (Fig. 2). There were also small solid areas in which the vascular nature of the lesion was not evident (Fig. 4) and areas which showed irregularly anastomosing vascular channels. These neoplastic cells had round or ovoid nuclei, one or two small nucleoli and pale eosinophilic cytoplasm (Fig. 3). A reticulin stain revealed a tubular vasoformative architecture. Cytological atypia was mild and mitotic rate was 1 per 50 high power fields. No atypical mitotic figures were seen. Some endothelial cells had hobnail or matchstick appearance. Adnexal structures were surrounded by, but not destroyed by the tumour. There was a prominent infiltrate of small lymphocytes and lymphoid follicules the proliferating vascular spaces (Fig. 2). The


1
2
3
4

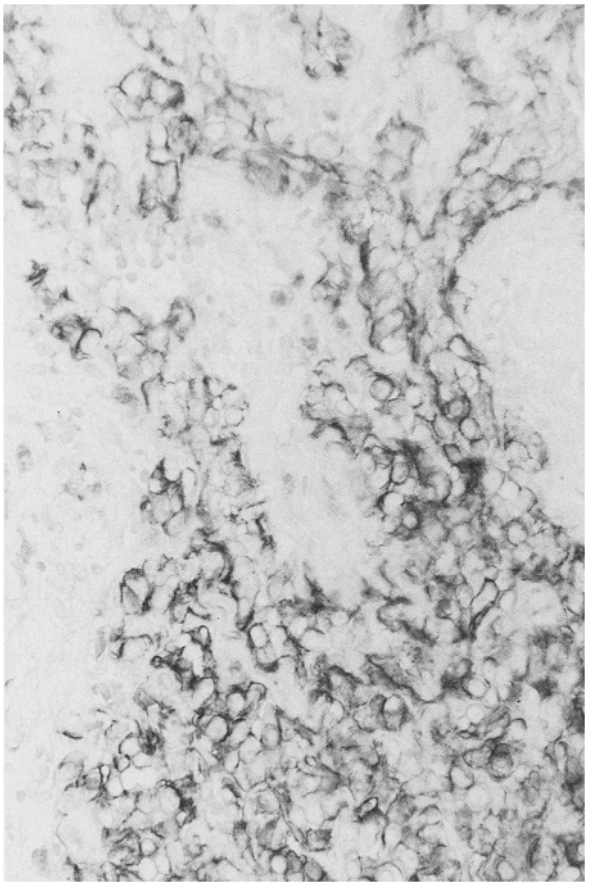


Fig. 5 CD31 immunoreactivity is observed in neoplastic cells of vasoforming and solid areas. ×200

stroma showed fibrosis with hyalinization and focal haemorrhage with haemosiderin deposition. The histology of the local recurrence was compatible with that of the primary lesion.

Immunohistochemical and flow cytometric findings

Many of neoplastic round vascular lining cells and cells in solid arrangements showed diffuse and strong positivity for vimentin (monoclonal; Amersham, Little Chalfont, UK; diluted 1:40) and CD31 (monoclonal: Dakopatts, Glostrup, Denmark: 1:20) and bound *Ulex europaeus* agglutinin 1 (UEA1; E.Y. Laboratories, San Mateo, Calif., USA; 1:25). Some neoplastic cells reacted positively with factor-VIII-related antigen (factor-VIII; polyclonal; Dakopatts: 1:500) and haematopoietic progenitor cell antigen CD34 (My 10; monoclonal; Becton Dickinson, Mountain View, Calif., USA; 1:25; Fig. 5). Alpha-smooth muscle actin (monoclonal; Dakopatts, 1:50), muscle specific actin, HHF35 (monoclonal; Enzo Diagnostics, New York, N.Y., USA; 1:50) and desmin (polyclonal; Bio-Science, Emmenbrucke, Switzerland; 1:50) were positive for pericytes around normal blood vessels, but these were uniformly negative around all the neoplastic blood vessels and in the solid areas. CAM5.2 (monoclonal; 39 kDa and 43 kDa; Becton Dickinson; 1:1) was negative in the neoplastic cells. Flow cytometric analysis using paraffin-embedded sections showed a diploidy DNA histogram with S-phase fraction of 9.0% and a coefficient of 5.8%.

Fig. 1 Diffuse and infiltrative neoplasm characterized by long arborizing blood vessels arranged in a retiform pattern. H & E, ×40

Fig. 2 A small lymphocytic infiltrate closely associated with arborizing blood vessels. H & E, ×100

Fig. 3 Neoplastic vessels lined by cuboidal, flattened, or hobnail-like endothelial cells. H & E, ×400

Fig. 4 A lobular arrangement of round neoplastic cells. H & E, ×200

Discussion

The histopathological features of our case are very similar to those previously reported as RH [1]. The tumour was characterized by a infiltrating growth pattern, arborizing blood vessels arranged in a retiform pattern lined by cuboidal and flattened cells, occasional hobnail appearance of endothelial cells and a prominent small lymphocytic infiltrate. However, this tumour differs from typical RHs in some respects. RHs typically occur in young and middle-aged adults although the original series [1] contained at least one elderly patient similar to this case. Histologically, endothelial hobnail features, which were considered to indicate differentiation toward high endothelial cells of post capillary venules [1], were less prominent in this case. Solid arrangements were observed near the neoplastic retiform vascular vessels, but neither cellular atypia nor mitotic figures were observed.

Our immunohistochemical study showed endothelial markers in the neoplastic cells and absence of a pericytic component within the neoplasm. Among antibodies used CD31 was the most sensitive and most specific for endothelial cells as De Young et al. [3] mentioned.

The main differential diagnosis includes cutaneous angiosarcoma, Dabska tumour (malignant endovascular papillary angioendothelioma) [2, 9], and angiomatosis. Cutaneous angiosarcoma has a very high rate of recurrence, metastasis and mortality [6]. Dissection of collagen is not a distinguishing feature of RH or cutaneous angiosarcoma. The lack of significant cellular atypia, mitotic activity, appendiceal destruction, and endothelial multilayering helps to differentiate RH from angiosarcoma. In contrast to Dabska tumour, RH appears most often in the extremities and trunk of young to middle-aged adults rather than in children. Retiform vascular proliferation is not usually observed in Dabska tumour. However, since RH and Dabska tumour have a similar biological behaviour and share many histological features, Calonje et al. [1] indicated that RH might represent the adult counterpart of RH.

RH can be easily differentiated from angiomatosis, which usually occurs in infants or young adults, is characterized by the involvement of a large segment of the body and consists of a melange of large venous, cavernous and capillary-sized vessels. Capillary-sized vessels are usually located in the wall or slightly adjacent to a large vein [10].

For cutaneous angiosarcomas histological differentiation is not considered to be an important prognostic factor with the exception of angiosarcoma of the breast [6]. There is evidence that a marked lymphocytic response

and lack of appendical destruction is associated with a better prognosis [7, 8]. It is assumed that some reported cutaneous angiosarcomas with relatively favorable outcome might have been RHs.

Recurrences of RH are common, but regional lymph node metastasis has been described in only one case and distant spread or tumour-related death has not been reported [1]. The current tumour was slow growing (the patient had a 10 year preoperative duration of the nodule) and local recurrence occurred 27 months after the excision. The tumour had a diploid DNA content with low S-phase fraction, probably indicating the overall benign nature or low-grade malignancy of the neoplasm [4, 5]. These findings support the view that RH is a low-grade angiosarcoma and indicate that RH must be distinguished from conventional angiosarcoma, which has a very high rate of recurrence, metastasis and mortality.

Acknowledgements The authors thank Masahi Sugimoto, Yukihiro Takeuchi and Tae Makino for their technical assistance and Michiko Takaki for preparation of the photographs.

References

1. Calonje E, Fletcher CDM, Wilson-Jones E, Rosai J (1994) Retiform hemangioendothelioma. A distinctive form of low-grade angiosarcoma delineated in a series of 15 cases. Am J Surg Pathol 18:115–125
2. Dabska M (1969) Malignant endovascular papillary angioendothelioma of the skin in childhood. Clinicopathologic study of 6 cases. Cancer 24:503–510
3. De Young BR, Wick MR, Fitzgibbon FJ, Sirgi KE, Swanson PR (1993) CD 31. An immunospecific maker for endothelial differentiation in human neoplasms. Appl Immunohistochem 1:97–100
4. Fukunaga M, Silverberg SG (1990) Kaposi's sarcoma in patients with acquired immune deficiency syndrome: a flow cytometric DNA analysis of 26 lesions in 21 patients. Cancer 66:758–764
5. Fukunaga M, Shimoda T, Nikaido T, Ushigome S, Ishikawa E (1993) Soft tissue vascular tumors. A flow cytometric DNA analysis. Cancer 71:2233–2241
6. Holden CA, Spitte MF, Wilson-Jones E (1987) Angiosarcoma of the face and scalp, prognosis and treatment. Cancer 59: 1046–1057
7. Jones EW, Holden CA (1984) A clinicopathological study of angiosarcoma of the face and scalp. Arch Dermatol 120:1611–1612
8. Maddox JC, Evans HL (1981) Angiosarcoma of skin and soft tissue: a study of forty-four cases. Cancer 48:1907–1921
9. Morgan J, Robinson MJ, Rosen LB, Unger H, Niven J (1989) Malignant endovascular papillary angioendothelioma (Dabska tumor). A case report and review of the literature. Am J Dermatopathol 11:64–68
10. Rao KV, Weiss SW (1992) Angiomatosis of soft tissue. An analysis of the histologic features and clinical outcome in 51 cases. Am J Surg Pathol 16:764–771
11. Weiss SW (1994) Histologic typing of soft tissue tumours, 2nd edn. (WHO, international histological classification of tumors) Springer, Berlin Heidelberg New York