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Angiosarcoma of the scalp: report of two cases with fatal pulmonary complications and a review of Japanese autopsy registry data *

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Summary. Two cases of angiosarcoma of the scalp were reported. The patients were elderly men and died from pulmonary complications, including pneumothorax, pulmonary haemorrhage and pneumonia, associated with metastatic tumours in the lungs. The data recorded from 95 autopsies of patients with angiosarcoma in Japan during 1980–1984 were analyzed. According to the anatomical distribution of the primary tumour, the patients could be subdivided into a scalp group and non-scalp group. In both groups, the most common metastatic site was the lung. The patients of the scalp group had more frequent pulmonary complications such as pneumonia, haemothorax, atelectasis and pneumothorax, when compared with the patients of the non-scalp group. In particular, pneumothorax was observed only in the patients of angiosarcoma of the scalp. The results indicate that angiosarcoma of the scalp tends to metastasize to the lung, especially to the subpleural or surface pleural area, and these metastatic tumours are prone to necrosis, causing characteristic pulmonary complications.

Key words: Angiosarcoma – Metastasis – Pulmonary complications – Pneumothorax

Introduction

Angiosarcoma of the skin occurs predominantly in the scalp and face of elderly patients (Enzinger and Weiss 1983; Hodgkinson et al. 1979; Lever and Schaumberg-Lever 1983; Maddox and Evans 1981) and is a highly malignant neoplasm, often metastasizing to several organs.

The clinical and pathological features of angiosarcoma of the skin have been characterized in several studies (Hodgkinson et al. 1979; Kitamura and Tamura 1978; Maddox and Evans 1981; Rosai et al. 1976). However, autopsy cases of angiosarcoma are few and have not been completely examined. The pathological data on angiosarcoma described in this report are based on an analysis of the data recorded in autopsies of 95 Japanese patients during the 5 year period from 1980–1984.

Report of cases

Case 1. A previously well 69-year-old man was admitted to hospital because of a subcutaneous tumour, 3 cm in diameter, in the right parietal area. He did not give a history of previous trauma. The tumour was removed and skin transplantation was performed. In the next six years, local recurrence occurred and tumours were removed several times. Thoracotomy was performed for recurrent pneumothorax and at the same-time, metastatic lymph nodes including left anteroauricular, left cervical, left hilar and right supraclavicular lymph nodes were removed.

On admission to the Tokyo Medical and Dental University Hospital, the patient was well nourished but complained of exertional dyspnoea, productive cough with massive sputum and right anterior chest pain. Voluminous expectation of yellowish clear jelly-like liquid (up to 200 ml daily) was observed. Laboratory studies revealed a haemoglobin level of 14.3 g/dl and a leukocyte count of 5100/mm^3 with a normal differential. Sodium level was 134 mEq/l (Normal 138–147) but other electrolytes, lactic dehydrogenase (LDH), serum transaminases (GOT, GPT), blood urea nitrogen (BUN), creatinin, bilirubin, glucose and serum protein levels were within normal ranges.

The chest radiographs revealed marked collapse of the left lung and multiple cystic nodular lesions of the bilateral lung. Cytology of the sputa and pleural effusion revealed malignant cells.

Despite several infusions of anticancer drugs (doxorubicin hydrochloride and Picibanil; freeze dried powder of streptococcus pyogenes) to the pleural cavity, as well as treatment of

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symptoms, the patient's condition deteriorated gradually. He died of respiratory failure about four months after the last admission.

Case 2. A previously healthy 61-year-old man was admitted to the Japan Red Cross Medical Center complaining of a subcutaneous tumour, 1 cm in diameter, of the right forehead. The patient received 40 Gy to the scalp. The therapy was not effective. One month later, physical examination revealed four metastatic nodules on the forehead and in the postauricular regions. The primary and metastatic tumours were removed. The patient was prescribed anticancer drugs (dimethyl-triazeno-imidasole carboxamide, vincristine sulphate and amino-methyl-pyrimidin-1-methyl-chlorethyl-nitrosoureahydrochloride).

Three months later, on the second admission, several subcutaneous nodules were found on the forehead. The patient was treated with identical anticancer drugs and radiotherapy (60 Gy). Chest radiographs revealed several metastatic nodules in both lungs and bone metastases to a rib. Haemoptysis occurred and the patient died from respiratory failure, six months after his initial presentation.

Materials and methods

Surgical and autopsy specimens were prepared in the usual manner for light microscopic examination with 10% formalin fixation. Paraffin-embedded tissue sections were stained by Si-Mung's avidin-biotin-peroxidase complex (ABC) method (Hsu et al. 1981) for identification of factor VIII-related antigen using primary rabbit antihuman sera. For electron microscopic examination of autopsy specimens, blocks were also fixed in phosphate buffered 2.5% glutaraldehyde, post fixed in 1% osmium tetroxide, dehydrated in alcohol, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined in an electron microscope (H-500, Hitachi, Tokyo, Japan).

For several decades, hospital autopsies in Japan have been registered; the findings are published annually in the Annual of the Pathological Autopsy Cases in Japan (APACJ), each volume of which contains details from about 20000 autopsies. A review of the volumes published from 1980 to 1984 was undertaken to identify all recorded cases of angiosarcoma. Pertinent details of the autopsy findings were extracted, translated, and tabulated. For statistical analyses, we used Student's *t*-test, chi-square contingency tables and Fisher's exact probability test.

Results

The features of the surgical specimens of the primary tumour in our two cases are so similar as to allow a common microscopic description. The tumour cells are predominantly located in the dermis, partly with extention into the subcutaneous tissue. The structure of the tumour varies considerably from place to place. In some areas, the tumour shows an angiomatous pattern which is characterized by the formation of dilated dermal channels of an obvious vascular nature. Anastomoses are frequent among them, resulting in the formation of an intricate network which dissects individual collagen fibers and surrounds cutaneous adnexa and subcutaneous fat lobules (Fig. 1a). The cells lining the lumena of the neoplastic vessels are spindle shaped and some of them are positively stained for factor VIII-related antigen immunohistochemically (Fig. 1b).

In other parts, the tumour cells show an undifferentiated pattern without forming easily recognizable vascular channels (Fig. 1c). The nuclei are larger than those of the cells of angiomatous areas; they have an oval shape, a plump appearance, a moderate amount of chromatin, a small nucleolus and frequent mitoses. An inflammatory reaction around the tumour is a prominent feature. The predominant cells are lymphocytes, often arranged in nodules and intermingled with histiocytes and plasma cells.

In Case 1, metastatic lesions were found in the both lungs and the lymph nodes of subclavian, paratracheal, mediastinal, and paraaortic regions. The pulmonary metastases were multiple. They were cystic nodules, 5 cm in diameter, with marked necrosis and liquefaction in the center. Microscopically, several tumours located in the subpleural area show invasion as far as the pleural tissue (Fig. 2a). The direct cause of death was respiratory failure due to a lipoid and partly organizing pneumonia. Pneumonia may be caused by recurrent collapse of the lung due to pneumothorax and the mechanical compression effect of metastatic tumours in the hilar lymph nodes. In Case 2, metastatic lesions were found in the lung, liver, kidney, stomach, small intestine, rib and vertebrae. Pulmonary haemorrhage with marked oedema was observed in both lungs. These conditions were fatal and were ascribed to the destruction of the vascular wall by the metastatic tumour in association with marked necrosis (Fig. 2b).

Electron microscopic examination of the metastatic tumours of the lung (Case 1) and the skin (Case 2) reveals Weibel-Palade bodies or pinocytotic vesicles in the cytoplasm (Fig. 3). In both cases, desmosomes and intracytoplasmic filaments varying in abundance are seen in several of the sections examined.

Recorded data from the autopsies of 95 patients with angiosarcoma were analyzed. Of these patients, 51 were men and 44 were women. Anatomical distribution of the primary site of the tumour was shown in Table 1. On the basis of the location of the primary, the patients were subdivided into two groups: a scalp and a non-scalp group. The ages of the patients were: scalp group, 74 ± 10 years; non-scalp group, 54 ± 19 years (mean $\pm$ SD) a difference which was highly significant ($P < 0.001$). Men outnumbered women in a ratio of 1.5:1 in the scalp group and the sex ratio was 1:1 in the non-scalp group.

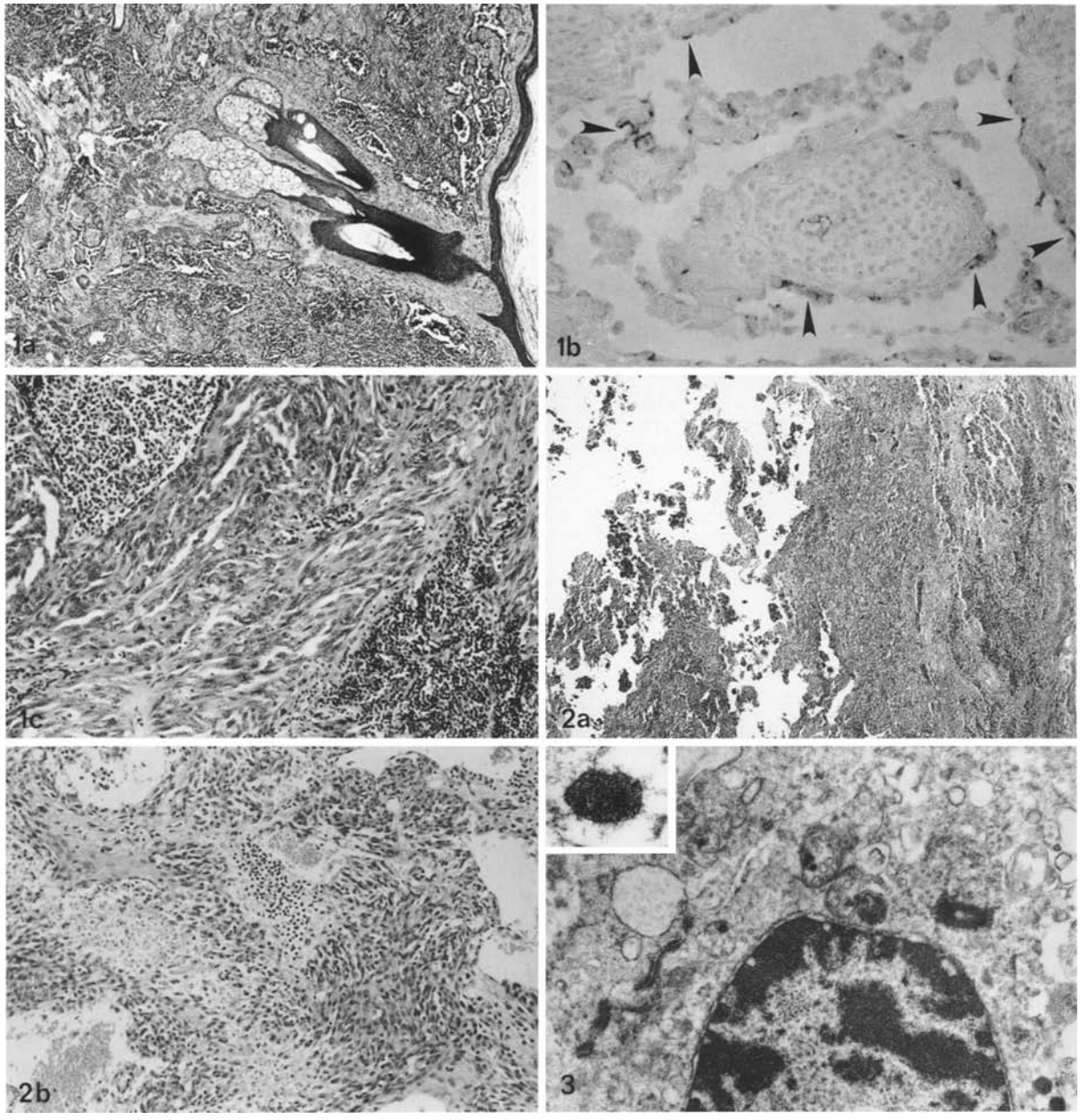

Fig. 1a–c. Primary tumour in Case 1. **a** Angiomatous area showing anastomosing channels lined by endothelial cells. Individual collagen fibers dissected by the tumour cells (Haematoxylin and eosin stain, ×56). **b** Some of the lining cells show positive immunostaining for factor VIII-related antigen (*arrows*) (×320). **c** Undifferentiated area showing a solid pattern of growth. The tumour cells have a polygonal shape reminiscent of epithelial cells. Frequent mitotic figures are also seen (HE ×100)

Fig. 2a, b. Pulmonary metastatic tumours in Case 1 *a* and Case 2 *b*. **a** Tumour cells of subpleural metastatic nodule of the lung showing invasion to the pleural tissue (*right side*) and cystic change (*left side*) (HE ×56). **b** Tumour cells showing patchy necrosis resulting in pulmonary haemorrhage (HE ×100)

Fig. 3. Electron micrographs showing desmosomes, pinocytotic vesicles and Weibel-Palade body (*inset*) of the tumour cell of pulmonary metastasis (Case 1, ×1000; Inset ×4000)

Anatomical distribution of metastases in the scalp group and the non-scalp group is shown in Table 2. Metastases occurred mainly in organs such as the lung, bone, liver, pleura, and lymph node. Pulmonary metastasis was the most frequent in both groups. Lymph nodal involvement in the non-scalp group was more common than that in the scalp group, but the difference was not statistically significant.

Pulmonary complications in the autopsy cases were shown in Table 3. Pneumonia was the commonest single pathological entity found both in

Table 1. Anatomical distribution of angiosarcoma in 95 Autopsy Cases (APACJ[a], 1980–1984)

Location	Number of cases	%
Scalp	33	34.7
Liver	17	17.9
Soft tissue	14	14.7
Bone	6	6.3
Spleen	5	5.3
Skin	4	4.2
Heart	3	3.2
Pleura	2	2.1
Pancreas	2	2.1
Stomach	2	2.1
Others	7	7.4
Total	95	100.0

[a] The Annual of the pathological autopsy cases in Japan

Table 2. Metastatic site of angiosarcoma

Scalp		Non-scalp	
Location	%	Location	%
Lung	79	Lung	61
Bone	42	Lymph node	40[a]
Liver	39	Liver	37
Pleura	30	Bone	31
Lymph node	21[a]	Pleura	21
Spleen	18	Spleen	16
GI tract	18	Kidney	16
Heart	12	Adrenals	13
Kidney	12	GI tract	11
Diaphragm	12	Diaphragm	10

[a] Metastasis to the lymph node was more frequent in the non-scalp group than in the scalp group ($X_1^2(0.1)=2.706<X^2=3.49<X_1^2(0.05)=3.841$)

Table 3. Pulmonary complications in autopsy cases of angiosarcoma

Complications	Scalp %	Non-scalp %
Pneumonia	31	18
Haemothorax	26*	7
Atelectasis	14	7
Pneumothorax	11*	0

Pulmonary complications are observed more frequently in the scalp group than in the non-scalp group. The differences are statistically significant for haemothorax and pneumothorax
* $P<0.01$)

the scalp and the non-scalp group, but may include non-specific pneumonia which occurs in the terminal stage. In contrast, haemothorax, atelectasis and pneumothorax were observed only in the cases with pulmonary metastasis. Although haemothorax, atelectasis and pneumothorax occurred in some of the patients of the scalp group, these conditions were rare in the patients of the non-scalp group. The differences were statistically significant ($P<0.01$).

Discussion

Angiosarcomas are malignant tumours of vascular origin which may occur in any region of the body. Several classifications of angiosarcomas have been proposed according to the location of the lesions, the history of trauma or irradiation, and the morphological features (Enzinger and Weiss 1983; Hodgkinson et al. 1979; Lever and Schaumberg-Lever 1983; Maddox and Evans 1981). Cutaneous angiosarcoma has been distinguished from others, because the tumour primarily affects the elderly and is usually located on the head and neck, particularly in the area of the scalp. The age of the patients of the scalp group in this study was 74 ± 10 years and the sex ration was 1.5:1. These data were similar to those of previous reports (Knight et al. 1980; Maddox and Evans 1981; Rosai et al. 1976; Wilson-Jones 1964). Compared with the analysis of 366 angiosarcomas reviewed at AFIP (Enzinger and Weiss 1983), angiosarcoma of the liver was more frequent and angiosarcoma of the breast was rarer in APACJ.

Some authors have stated that metastases to the cervical lymph nodes and haematogenous metastases to the lung and liver often occurs in angiosarcoma of the scalp and face (Lever and Schaumberg-Lever 1983; Maddox and Evans 1981). According to our review of the APACJ, haematogenous metastases were frequent both in the cases of angiosarcoma of the scalp and the non-scalp group, whereas metastases to the lymph nodes were more common in the non-scalp angiosarcoma.

Several cases of angiosarcoma of the scalp with pneumothorax and haemothorax have been reported (Cardozo et al. 1966; Kitamura and Tamura 1978; Loni et al. 1983; Simon et al. 1980). It has been said that the occurrance of spontaneous pneumothorax in association with metastatic disease to the lung should suggest sarcoma as the primary tumour – especially osteogenic sarcoma in children (Fraser and Paré 1970; Janetos and Ochsner 1963; Spittle et al. 1963). But several pulmonary metastatic tumours of other primary sites have also been reported as the cause of pneumothorax (Dines et al. 1973; Khan and Seriff 1973; Williams and Kidner 1971; Yeung and Bonnet 1977). The mechanism of the development of spontaneous pneumothorax in metastatic sarcoma has been described as a rupture of peripheral necrotic tu-

mour into a bronchus and the pleural space, creating a broncho-pleural fistula (Dines et al. 1973). Another possibility may be tumour embolus with infarction of the lung forming the air leak (Dines et al. 1973). In our cases, metastatic nodules of the lung were predominantly composed of solid tumours with little vasoformative activity. Therefore, the nodules are prone to necrosis resulting from spontaneous vascular occlusion with the tumour, with possible formation of a broncho-pleural fistula. Neither tumour emboli nor pulmonary infarction were observed in our cases.

Girard et al. (1970) have reported that in cases of angiosarcoma of the scalp, death results from destructive ulceration of the primary tumour of the scalp rather than metastases. However, in our two cases pulmonary metastases caused death from respiratory failure. Further, according to the APACJ, pulmonary complications occurred more frequently in cases of angiosarcoma of the scalp than in the non-scalp angiosarcoma. Therefore, pulmonary metastases are of great value in determining the prognosis of the patient with angiosarcoma of the scalp.

Factor VIII-related antigen has been used as a marker for neoplasms of endothelial origin (Burgdorf et al. 1981; Guarda et al. 1982; Kitagawa et al. 1985). Guarda et al. (1982) have reported that eight of eleven cases of angiosarcoma of the head and neck show positive immunostaining for factor VIII-related antigen, but that solid areas of the tumour failed to show positive staining. Berry and Amerigo (1980) have stated that immunostaining with blood group antigens (BGA), markers for vascular tumours, may be helpful in identifying cells of endothelial origin but loss of BGA are observed in neoplastic cells. In our cases, positive immunostaining for factor VIII-related antigen is observed in the angiomatous area of the primary tumour and not in the undifferentiated area and the metastatic tumour. However, electron microscopic examination of the metastatic nodule revealed Weibel-Palade bodies or pinocytotic vesicles in the tumour cells. Rosai et al. (1976) have reported that clumps of filaments and pinocytotic vesicles are still present in the undifferentiated area of the angiosarcoma. Electron microscopic examination is surely useful for the diagnosis of angiosarcoma.

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