Pergamon

European Journal of Cancer, Vol. 35, No. 3, pp. 433–437, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(98)00299-8

Original Paper

Pilomatrix Carcinoma with Multiple Metastases: Report of a Case and Review of the Literature

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Pilomatrix carcinoma, the malignant counterpart of pilomatrixoma, is rare, with only 55 cases reported, and only four cases with visceral metastases described in the literature. Here we present a case report and a literature review on this rare tumour. A 74-year-old male with a pilomatrix carcinoma from the left temporal region presented in July 1996 and the tumour was excised. One month after diagnosis, metastases to both lungs and to a regional lymph node were found and histologically verified. The patient also developed metastases in the abdomen, back and thoracic spine. The latter resulted in spinal cord compression and paraplegia. Despite systemic chemotherapy with intravenous cisplatin and 5-fluorouracil and localised radiotherapy to the thoracic spine, progression and deterioration led to death within 3 months from time of diagnosis. Pilomatrix carcinomas are usually indolent. In our patient, however, the malignant disease progressed rapidly and it appeared to be resistant to both chemotherapy and irradiation. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: pilomatrix carcinoma, treatment, outcome, radiology, morphology
Eur J Cancer, Vol. 35, No. 3, pp. 433–437, 1999

INTRODUCTION

PILOMATRIXOMA WAS first described in 1880 by Malherbe and Chenantais [1] as a 'calcifying epithelioma', initially thought to be derived from sebaceous glands. In 1949, Lever and Griesemer [2] suggested that the origin of the tumour was hair matrix cells. Later, light and electron microscopic observations and histochemical studies have supported this view [3–6] and the name 'pilomatrixoma', first proposed by Forbis and Helwig [7] in 1961, has been generally accepted. Pilomatrixomas are slow-growing, benign dermal tumours with possible extension to the subcutaneous (s.c.) tissue [8].

Although the locally aggressive behaviour of some cases of pilomatrixoma was first suggested by Gromiko in 1927 [9], for decades it was considered a neoplasm in which malignant transformation did not occur [3]. The malignant variant of pilomatrixoma was not seriously considered until 1980, when Lopansri and Mihm [10] reported a case of aggressive pilomatrixoma and reviewed five similar cases from the literature. They proposed the term 'pilomatrix carcinoma' or 'calcifying epitheliocarcinoma of Malherbe'. Pilomatrix carcinoma is rare and hitherto 55 cases have been reported [11–18].

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Received 14 May 1998; accepted 16 Jul. 1998.

Recurrences of pilomatrix carcinomas are common, but the metastatic potential has not been acknowledged by all investigators dealing with this malignancy [19, 20]. Metastasising pilomatrix carcinoma is exceedingly rare, with only four reported cases in the literature [12, 21–23].

We present a case of pilomatrix carcinoma in a 74-year-old male in whom metastases to the neck, both lungs, thoracic spine and possibly the abdomen developed within a few months. The cancer showed an aggressive course with primary resistance to both chemotherapy and radiotherapy.

CASE REPORT

History

A 74-year-old male presented in July 1996 with a tumour in the left temporal region, which had been first noticed 2 months earlier. The patient had a previous history of occasional alcohol abuse and a lumbar disc herniation in 1977, but was otherwise healthy. The tumour, 4×3 cm and elevated 1 cm above the skin surface, was excised mid July. Skin was transplanted from the left upper arm to cover the defect. The histological diagnosis was pilomatrix carcinoma with non-radical surgical margins. For a planned wide excision, the patient was referred to the Department of Plastic Surgery in August 1996.

Examinations

At admittance, the examining doctor found a 1 cm large tumour beneath the transplant, suspicious of a local recurrence and an enlarged occipital lymph node. This time the patient commented on relatively severe interscapular pain that had lasted for approximately 2 months. He underwent a diagnostic work-up with plain chest X-ray, abdominal ultrasound, computer tomography (CT) scan of the chest, abdomen and pelvic area and bone scan. The chest X-ray revealed multiple lesions suspicious of lung metastases. The findings of the CT scan of the chest (Figure 1a) were consistent with multiple lung metastases. The abdominal ultrasound and the CT scan of the abdomen and pelvis (Figure 1b) demonstrated a 4×2 cm tumour with some central necrosis located in the right perirenal region. The bone scan was negative. Wide excision of the local tumour, excision of the enlarged lymph node in the left occipital region and CT-guided biopsy of one of the lung metastases were performed. Histologically, the tumour in the left temporal region was a recurrence of the previously excised pilomatrix carcinoma. The occipital lymph node and lung biopsy were both consistent with metastasis from pilomatrix carcinoma.

Pathological findings

On gross examination, the primary tumour measured 4×3 cm and was raised 1 cm above the surrounding skin. It had a brown surface and a white cut surface. Microscopic examination revealed a denuded surface with underlying sheets and nests of basaloid cells with abrupt transition to central areas with pycnotic cells and shadow cells (Figure 2a). Calcification was not seen. The basaloid cells had hyperchromatic nuclei with clumped chromatin, moderate pleomorphism, one to three distinct nucleoli (Figure 2b) and numerous mitoses, some of which were atypical. The mitotic rate was approximately 75 per 10 high power fields (35/mm^2). Immunocytochemical staining with Ki-67 showed a proliferation rate of 50%. Bcl-2 was expressed in 3% and p53 in 36% of the tumour cells. Low-molecular weight cytokeratin (CK-19) was strongly positive, whereas high-molecular weight cytokeratin (34βE12) was positive in scattered single cells only. Staining for HMB-45, S-100 and neurofilaments were negative. The tumour infiltrated deeply into the subcutaneous (s.c.) fat and to the deep surgical margin. No vascular or perineural infiltration was identified. The re-excision specimen was 4 cm wide and contained a 9 mm tumour rest with free surgical margin. The occipital lymph node (Figure 3a) and the lung biopsy (Figure 3b) both contained

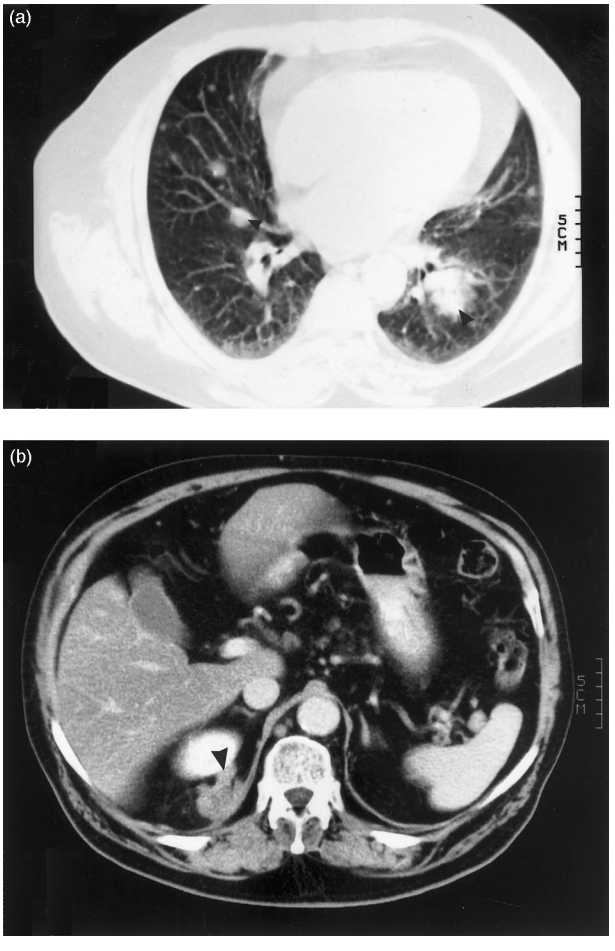

Figure 1. (a) Continuous 10 mm axial CT scans through the thorax showed a metastasis located centrally in the left lung (large arrow) and multiple smaller metastasis in the right lung parenchyma (small arrow). (b) Contrast enhanced continuous axial CT scans through the abdomen and pelvis revealed a tumour located between the apical part of the right kidney and the diaphragm (arrow).

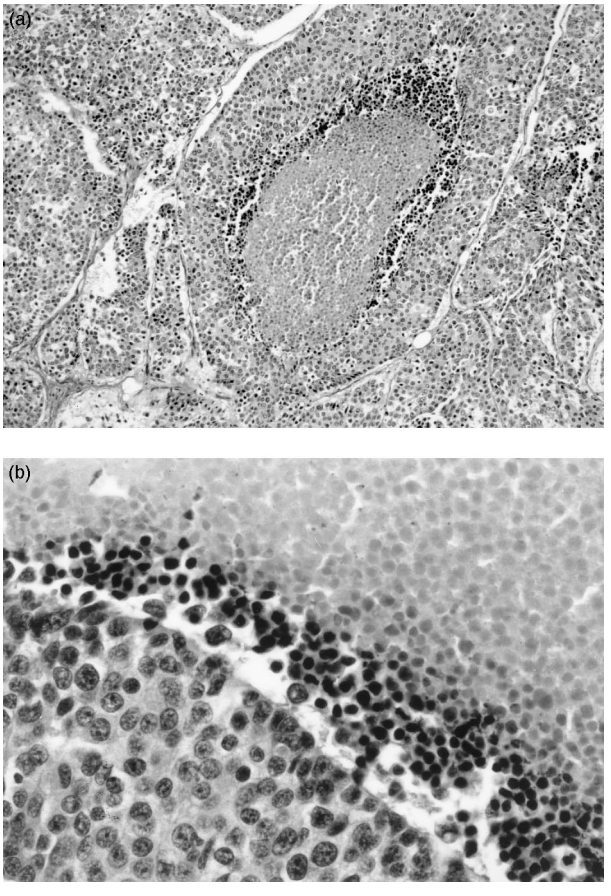

Figure 2. (a) The primary tumour with irregular nests of basaloid epithelial cells with a central area of pycnotic and shadow cells. (H&E, original magnification ×30). (b) Detail from the primary tumour with basaloid, pycnotic and shadow cells. The nuclei of the basaloid cells show moderate pleomorphism, clumped chromatin, and distinct nucleoli. (H&E, original magnification ×120).

tumour tissue with histological and immunocytochemical features similar to those of the primary tumour; both showing the characteristic shadow cells. As compared with the primary tumour, the Ki-67 proliferation rate was increased to 58%, p53 positivity to 50–60%, and bcl-2 to 12% in the metastases.

Treatment and outcome

During early September, chemotherapy treatment was initiated with the combination regimen of intravenous (i.v.) cisplatin and i.v. 5-fluorouracil (cisplatin 200 mg day 1 and 5-FU 2000 mg/24 h days 1–5). One week later, the patient's gait gradually deteriorated. Clinical examination revealed paraparesis and eventually the patient developed bladder paresis. Magnetic resonance imaging (MRI) showed a metastasis in the Th1 vertebra, penetrating into the spinal canal and compressing the spinal cord (Figure 4a). Metastases were also found in the Th9 vertebra and retro-/paravertebrally in the mid thoracic area (Figure 4b). The patient received high-dose steroid therapy (dexamethasone) followed by radiotherapy. The target volume encompassed C6 to Th3. Irradiation was given as a single posterior photon field (prescribed depth 40 mm) in 4 Gy fractions to a cumulated dose of 28 Gy. However, during radiation therapy, the patient developed complete paraplegia. A few days after completion of the radiotherapy, the patient suffered a severe pneumonia. In spite of i.v. antibiotic treatment, his condition deteriorated and he died at the beginning of October. At no stage had there been any sign of tumour regression. His relatives refused a request for an autopsy to be performed.

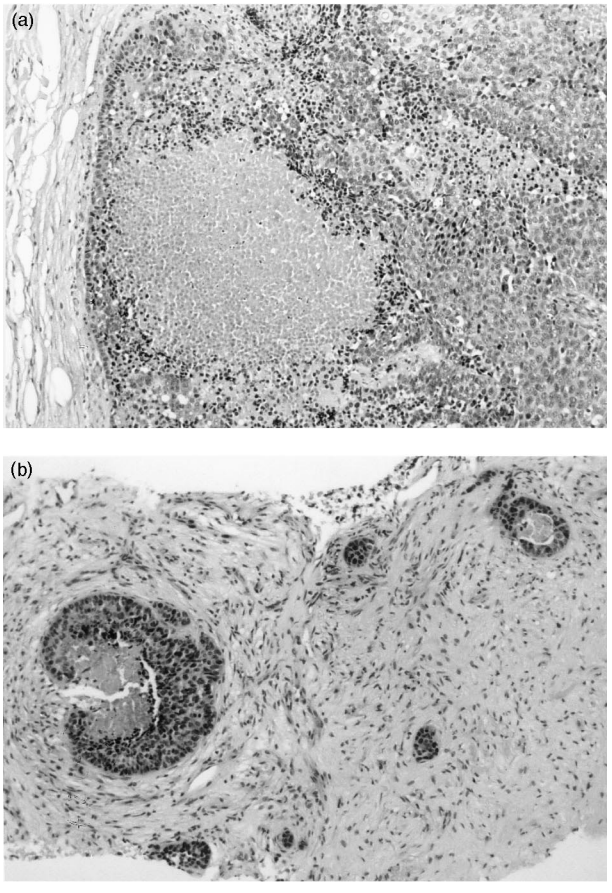

Figure 3. (a) Lymph node metastasis with basaloid, pycnotic and shadow cells. (H&E, original magnification ×30). (b) Lung biopsy showing fibrous tissue with nests of basaloid cells with central pycnotic and shadow cells. (H&E, original magnification ×30).

DISCUSSION

Although Gromiko even in 1927 [9] noted the aggressive behaviour of some pilomatrixomas, this tumour was considered to be benign without any malignant potential [3]. Surgical reports [24–26], during the 1970s, of locally aggressive pilomatrixomas led to the introduction of the terms 'pilomatrix carcinoma' and 'calcifying epitheliocarcinoma' by Lopansri and Mihm [10] in 1980. Their malignant terms were based on a review of five cases of 'pilomatrixoma with aggressive behaviour' and a case of their own. They noted that the presence of hyperchromatic, vesicular basaloid cells with numerous mitoses and infiltration into adjacent tissue or blood vessels correlated with aggressive clinical behaviour [10]. Subsequently, there have been an increasing number of reports of malignant pilomatrixomas.

Histologically, pilomatrix carcinoma is formed by irregular shaped cellular bands and sheets of basaloid cells. In the centre, necrosis, keratin and shadow cells are often seen. The nests of shadow cells may be calcified or show amyloid deposits [18, 27, 28]. The basaloid cells have hyperchromatic nuclei and prominent nucleoli [6, 29]. Mitoses vary between 12 and 62 per 10 high power field (HPF) and may be atypical [11]. Squamous cells and clear or transitional cells may also be seen, but are less numerous and show fewer nuclear abnormalities. The major clinical problem may be in distinguishing this rare malignant tumour from the more frequent benign pilomatrixomas. Both immunohistochemical and flow cytometric analyses have been performed to establish whether these methods may be used to differentiate pilomatrix carcinomas from its benign counterpart [16, 30]. Since neither of these methods have been successful, the pathologists will still have to rely on traditional morphological methods to diagnose pilomatrix carcinoma. The main indicators of malignancy in pilomatrixomas appear to be nuclear pleomorphism, frequent and atypical mitoses, central necrosis, infiltration of skin and soft tissue, blood and lymphatic vessel infiltration, and ulceration [12, 18, 31].

To date, 55 cases of pilomatrix carcinoma has been reported [6, 9–18, 21–26, 29–44]. Among these patients, there was a preponderance of males (78%), yielding a male:female ratio of 3:1. The majority of patients were older than 40 years (61%) with a mean age of 46 years (range 8–88 years). The tumours were located mainly in the head and neck region (65%), on the upper extremities (14%), or on the trunk (14%) and the mean tumour size was 4.2 cm (range 1–20 cm). Predilection for the head and neck area, upper extremity and upper back is similar for both the malignant and the benign lesion. Contrary to the pilomatrix carcinoma, the benign lesion occurs predominantly in females (male: female = 2/3) and in children and young adults (60% below 20 years) [11, 27]. Although the common opinion has been that pilomatrixomas in general are smaller than pilomatrix carcinomas, no correlation between size and malignancy has been demonstrated [10, 11, 32].

Pilomatrix carcinomas are locally aggressive tumours that have a tendency to recur. In the previously reported cases, follow-up data were available in 43 patients with regard to recurrences. Of these, the tumour relapsed in 21 patients (49%). It appears that simple excision may be a suboptimal

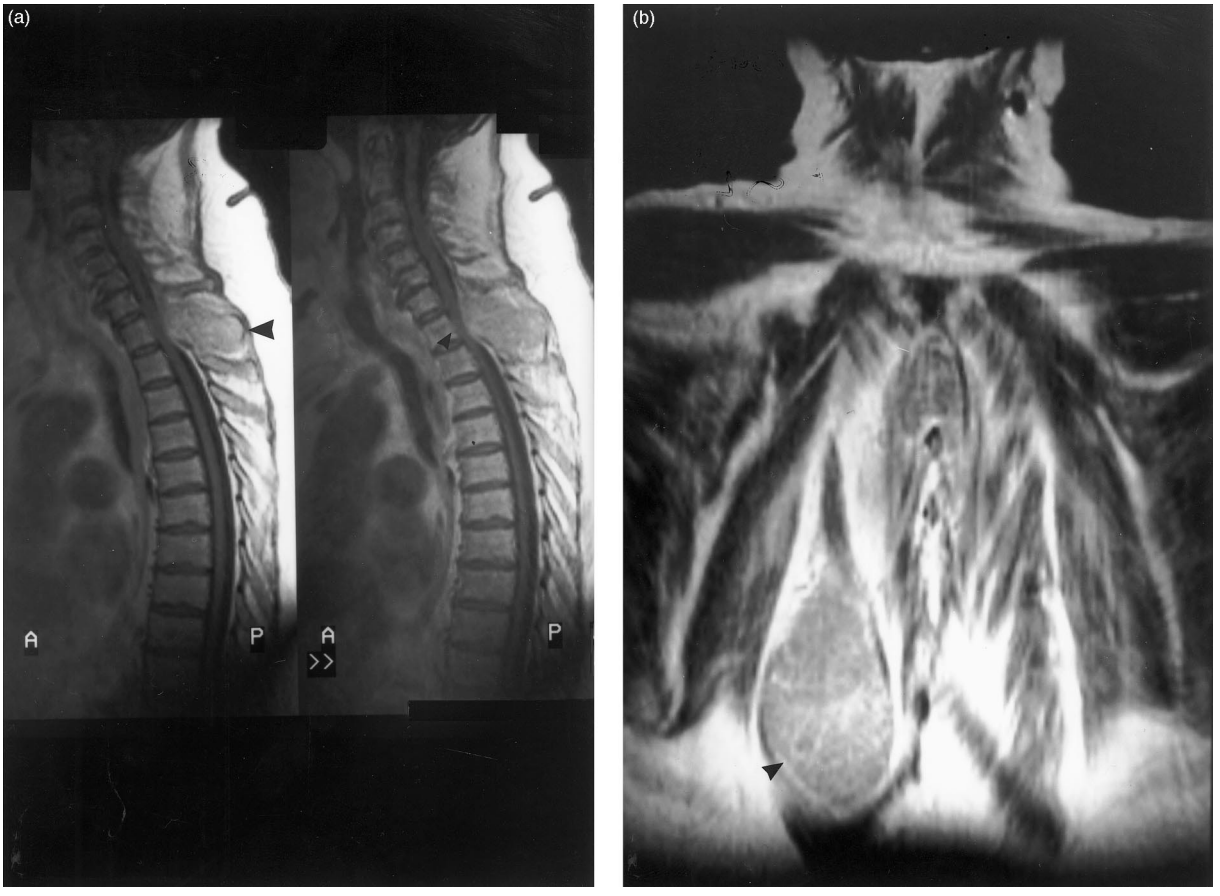

Figure 4. (a) Contrast enhanced sagittal T1 weighted MRI image (WI) through the thoracic spine showed tumour penetrating into the spinal canal, extradurally at the level of Th1 (large arrow). The tumour compressed the medulla (small arrow) from behind. The arch and pedicles were destroyed at this level. (b) Contrast enhanced coronal T1WI MRI image showed a tumour located in-between muscle groups to the right of the mid thoracic area (arrow).

surgical strategy for pilomatrix carcinomas as 67% (18/27) of the patients operated with this method relapsed. Thus, after the diagnosis of pilomatrix carcinoma has been established, a re-excision with adequate margins is indicated [11]. The role of radiotherapy is unclear due to limited experience with the modality used in this setting. However, 4 patients that received initial radiotherapy or underwent surgery followed by radiotherapy did not experience tumour recurrence [11, 35, 38]. In patients in whom wide excision is not possible, radiotherapy should be considered [11, 18, 33].

To our knowledge, only 4 patients with visceral metastases from pilomatrix carcinoma have been reported to date [12, 21–23]. In 1984, Gould and co-workers [21] reported the first case of metastatic pilomatrix carcinoma in a 67-year-old male. Within 4 years from the initial surgical excision on the back, the patient developed bilateral pulmonary metastases that were histologically confirmed. The patient was then lost to follow-up. In 1986, the case of a 52-year-old man with recurrent pilomatrix carcinoma of the right forearm and subsequent axillary node metastases and bilateral pulmonary metastases was described by Mir and associates [22]. Irradiation to the mediastinum and both hilar regions gave a dramatic, but temporary effect, whereas two different chemotherapy regimens failed to control the metastatic disease. Two and a half years after diagnosis the patient died from extensive metastatic disease involving the heart, liver and kidney. In 1993, a case of bone metastasis (right superior pubic ramus) developing 2 years after excisions of recurrent pilomatrix carcinoma in the thigh in a 31-year-old male was published by O'Donovan and colleagues [23]. The diagnosis was confirmed by a biopsy of the pubic metastasis. There are, however, no data on further therapy or treatment outcome in this patient. Niedermeyer and colleagues in 1996 [12] described a 50-year-old male with malignant pilomatrixoma at the right base of the neck. Two months later the patient developed multiple metastases in the lungs and in the sternum. Despite two different chemotherapy regimens, there was progression of the metastatic disease. Shortly after, the patient developed generalised seizures and cerebral metastases were demonstrated on CT scans. 18 months after the initial diagnosis, the patient died of metastatic disease to the heart, lungs, liver, pancreas, gastric and colorectal mucosa, kidney, adrenal gland, brain, bone and skin (confirmed at autopsy).

Our case was initially diagnosed with a pilomatrix carcinoma as it possessed the features suggested by Lopansri and Mihm [10]. Consistent with the previous reports [12, 21–23], our case demonstrated that malignant pilomatrixomas are capable of metastasising and, moreover, illustrated the highly aggressive biological behaviour of the metastatic lesions. Within 2 months of diagnosis, the pilomatrix carcinoma had metastasised to regional lymph nodes, lungs, thoracic spine, and possibly to the right perirenal region. In accordance with treatment data reported in two previous cases [12, 22], the malignant lesions appeared primary resistant to both chemotherapy and irradiation.

1. Malherbe A, Chenantais J. Note sur l'epitheliome calcifie des glandes sebaces. *Prog Med* 1880, 826–837.
2. Lever WF, Griesemer RD. Calcifying epithelioma of Malherbe. *Arch Dermatol* 1949, **83**, 506–518.
3. Lever WF, Schaumburg-Lever G. *Histopathology of the Skin. 5th edn*. Philadelphia, JB Lippincott, 1975, 518–520.
4. Hashimoto K, Nelson RG, Lever WF. Calcifying epithelioma of Malherbe: histochemical and electron microscopic studies. *J Invest Dermatol* 1966, **46**, 391–408.
5. Headington JT. Tumors of the hair follicle. *Am J Pathol* 1976, **85**, 480–505.
6. Tateyama H, Eimoto T, Tada T, *et al*. Malignant pilomatrixoma. An immunohistochemical study with antihair keratin antibody. *Cancer* 1992, **69**, 127–132.
7. Forbis Jr R, Helwig EB. Pilomatrixoma (calcifying epithelioma). *Arch Dermatol* 1961, **83**, 606–618.
8. LeBoit PE, Parslow TG, Choy S-H. Hair matrix differentiation. Occurrence in lesions other than pilomatricoma. *Am J Dermathopathol* 1987, **9**, 399–405.
9. Gromiko N. Zur kenntnis der bøsartigen Umwandlung des verkalkten Hautepithelioms. *Arch Pathol Anat* 1927, **265**, 103–116.
10. Lopansri S, Mihm MC. Pilomatrix carcinoma or calcifying epitheliocarcinoma of Malherbe: a case report and review of literature. *Cancer* 1980, **45**, 2368–2373.
11. Sau P, Lupton G, Graham JH. Pilomatrix carcinoma. *Cancer* 1993, **71**, 2491–2498.
12. Niedermeyer HP, Peris K, Hofler H. Pilomatrix carcinoma with multiple visceral metastases. Report of a case. *Cancer* 1996, **77**, 1311–1314.
13. Martelli G, Giardini R. Pilomatrix carcinoma: a case report and review of the literature. *Eur J Surg Oncol* 1994, **20**, 703–704.
14. McCulloch TA, Singh S, Cotton DW. Pilomatrix carcinoma and multiple pilomatrixomas. *Br J Dermatol* 1996, **134**, 368–371.
15. Sabharwal BD, Malhotra V. Pilomatrix carcinoma—calcifying epitheliocarcinoma of Malherbe. *Indian J Pathol Microbiol* 1994, **37**, 45–46.
16. Panico L, Manivel JC, Pettinato G, *et al*. Pilomatrix carcinoma. A case report with immunohistochemical findings, flow cytometric comparison with benign pilomatrixoma and review of the literature. *Tumori* 1994, **80**, 309–314.
17. Zagarella SS, Kneale KL, Stern HS. Pilomatrix carcinoma of the scalp. *Australas J Dermatol* 1992, **33**, 39–42.
18. Monchy D, McCarthy SW, Dubourdieu D. Malignant pilomatrixoma of the scalp. *Pathology* 1995, **27**, 201–203.
19. Murphy GF, Elder DE. Malignant tumors with pilosebaceous differentiation. In *Atlas of Tumor Pathology. Third Series Fascicle 1*. Washington DC, Armed Forces Institute of Pathology 1991, 147–148.
20. Gibbon DH, McKee PH. Tumours of the epidermal appendages. In McKee PH, ed. *Pathology of the Skin with Clinical Correlations*. London, Gower Medical Publishing 1989, 15.23–15.25.
21. Gould E, Kurzon R, Kowaczyk AP, *et al*. Pilomatrix carcinoma with pulmonary metastasis. *Cancer* 1984, **54**, 370–372.
22. Mir R, Cortes E, Papantoniou P, *et al*. Metastatic tricomatrical carcinoma. *Arch Pathol Lab Med* 1986, **110**, 660–663.
23. O'Donovan DG, Freemont AJ, Adams JE, *et al*. Malignant pilomatrixoma with bone metastasis. *Histopathology* 1993, **23**, 385–386.
24. Krausen AS, Ansel DG, Mays BR. Pilomatrixoma masquerading as a parotid mass. *Laryngoscope* 1974, **84**, 528–538.
25. Rothman D, Kendall AB, Baldi A. Giant pilomatrixoma (Malherbe calcifying epithelioma). *Arch Surg* 1976, **111**, 86–87.
26. Sasaki CT, Yue A, Enriques R. Giant calcifying epithelioma. *Arch Otolaryngol* 1976, **102**, 753–755.
27. Marrogi AJ, Wick MR, Dehner LP. Pilomatrical neoplasms in children and young adults. *Am J Dermatopathol* 1992, **14**, 87–94.
28. Sano Y, Mihara M, Miyamoto T, *et al*. Simultaneous occurrence of calcification and amyloid deposit in pilomatricoma. *Acta Derm Venereol* 1990, **70**, 256–259.
29. Miyahara H, Imayama S, Hashizume T, *et al*. Two cases of pilomatrix carcinoma. *J Dermatol* 1990, **17**, 322–325.
30. Manivel C, Wick MR, Mukai K. Pilomatrix carcinoma: an immunohistochemical comparison with benign pilomatrixoma and other benign cutaneous lesions of pilar origin. *J Cutan Pathol* 1986, **13**, 22–29.
31. Green E, Sanusi D, Fowler MR. Pilomatrix carcinoma. *J Am Acad Dermatol* 1987, **17**, 264–270.
32. Krugman ME, Bansberg S, Strout E. Pilomatrical carcinoma. *Plast Reconstr Surg* 1990, **86**, 340–343.
33. Chen KTK, Taylor DR. Pilomatrix carcinoma. *J Surg Oncol* 1986, **33**, 112–114.
34. Pradetsky AP, Yuzvinkevich AK. Malherbe's epithelioma with signs of malignization. *Arch Pathol* 1969, **31**, 64–66.
35. Weedon D, Bell J, Mayze J. Matrical carcinoma of the skin. *Cutan Pathol* 1980, **7**, 39–42.
36. Van der Walt JD, Rohlova B. Carcinomatous transformation in a pilomatrixoma. *Am J Dermatopathol* 1984, **6**, 63–69.
37. Wood MG, Parhizgar B, Beerman H. Malignant pilomatrixoma. *Arch Dermatol* 1984, **120**, 770–773.
38. Veliath AJ, Reddy KS, Gomathinayagam D. Malignant pilomatrixoma: report of a case. *Acta Radiol Oncol* 1984, **23**, 429–431.
39. Nield DV, Saad MN, Ali MH. Aggressive pilomatrixoma in a child: a case report. *Br J Plast Surg* 1986, **39**, 139–141.
40. Lineaweaver WC, Wang TN, Leboit PL. Pilomatrix carcinoma. *J Surg Oncol* 1988, **37**, 171–174.
41. Rabkin MS, Witter CT, Soong VY. Flow cytometric DNA content analysis of a case of pilomatrix carcinoma showing multiple recurrences and invasion of the cranial vault. *J Am Acad Dermatol* 1990, **23**, 104–108.
42. Bridger L, Koh HK, Smiddy M, *et al*. Giant pilomatrix carcinoma: report and review of the literature. *J Am Acad Dermatol* 1990, **23**, 985–988.
43. Aloi FG, Molinero A, Pippione M. Basal cell carcinoma with matrical differentiation. Matrical carcinoma. *Am J Dermatopathol* 1988, **10**, 509–513.
44. Campoy F, Stiefeol P, Stiefel E, *et al*. Pilomatrix carcinoma: role played by MR imaging. *Neuroradiology* 1989, **31**, 196–198.

Acknowledgement—The financial support from the Norwegian Cancer Society is greatly appreciated.