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Clinical Record

Spindle cell carcinoma arising in the pharynx, with granulocytosis and high serum granulocyte colony stimulating factor titre

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Abstract

We report the case of a 67-year-old man with a left pharyngeal tumour, whose peripheral blood showed granulocytosis (white blood cell count, 58 300/μl) and a high serum granulocyte colony stimulating factor titre (184 pg/ml). The tumour showed pleomorphic proliferation of atypical spindle cells in a myxomatous stroma, revealing a sarcomatous pattern. The spindle-shaped neoplastic cells had irregularly shaped nuclei, a thick nuclear membrane, prominent eosinophilic nucleoli and abundant cytoplasm. They strongly expressed wide-spectrum keratin, cytokeratins (CAM5.2, MNF116), vimentin and vascular endothelial growth factor. A few neoplastic cells expressed granulocyte colony stimulating factor. A spindle cell carcinoma was diagnosed. This may be the first documented case of a granulocyte colony stimulating factor producing cancer arising in the pharynx. The patient died four months after the initial symptoms appeared.

Key words: Pharynx; Spindle Cell Carcinoma; Granulocyte Colony Stimulating Factor

Introduction

Spindle cell carcinomas have been reported in several organs: the lung, pancreas, thymus, prostate, urinary bladder, breast and penis. Spindle cell carcinomas arising in the larynx are extremely rare.[1] Only three cases appear in the large collection of the US Armed Forces Institute of Pathology.[2] These tumours develop aggressively and have a poor prognosis.

Carcinomas which produce granulocyte colony stimulating factor may arise in several organs, especially the lung, stomach, liver, thyroid gland, gall bladder, urinary bladder, thymus and cervix. Most granulocyte colony stimulating factor producing carcinomas are poorly differentiated or undifferentiated and have a poor prognosis.

We report the case of an aggressive spindle cell carcinoma arising in the pharynx, with granulocytosis and a high serum granulocyte colony stimulating factor titre, in a 67-year-old man.

Case report

A 67-year-old man noticed nasal obstruction, pharyngeal pain and hoarseness in July 2003. During the next month, he expectorated a tumour-like fragment, which was not examined pathologically. He visited our hospital because of tumour enlargement.

The tumour was seen to occupy the pharynx but had caused neither respiratory failure nor dysphagia.

Laboratory findings on admission were as follows: white blood cell (WBC) count, 25 800/μl; stab leukocyte, 13.0 per cent; segmented leukocyte, 76.0 per cent; and serum granulocyte colony stimulating factor titre, 184 pg/ml (normal range, <1.8 pg/ml).

Computed tomographic angiography showed an irregularly enhanced mass in the left pharynx that completely filled the pharynx. Magnetic resonance imaging with gadolinium revealed a poorly enhancing mass on T1-weighted images and a strongly enhancing mass on T2-weighted images, in the middle pharynx, with multiple cervical lymph node metastases.

An incisional biopsy performed at the beginning of September 2003 yielded a 13 × 8 mm specimen.

Tracheotomy was performed to prevent respiratory failure. The patient underwent chemotherapy (6 mg/day of cisplatin) and radiotherapy (total radiation dose of 60 Gy). The WBC count decreased from 47 600 to 11 200/μl during therapy, and the therapeutic effect was relatively good. However, left subclavicular lymph node metastases developed at the end of October 2003, and in November the WBC increased to 58 300/μl. Chest radiography showed multiple coin lesions in the lungs and pleural effusion.

The patient died four months after the initial symptoms appeared. No autopsy was performed.

Pathological results

The tumour showed proliferation of atypical spindle and pleomorphic cells in a myxomatous stroma, revealing a sarcomatous pattern (Figure 1). Abnormal mitotic cells were frequently observed. The neoplastic cells had irregularly shaped nuclei, a thick nuclear membrane, large

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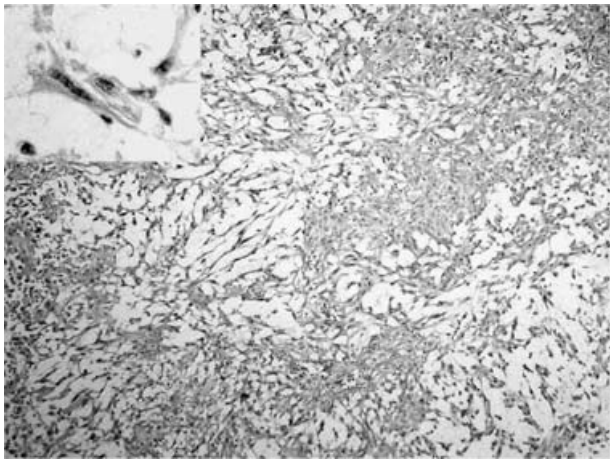

FIG. 1

The tumour, showing proliferation of atypical spindle-shaped and pleomorphic cells in a myxomatous stroma (H&E; ×100; inset ×400).

eosinophilic nucleoli and abundant, periodic acid–Schiff positive cytoplasm.

The neoplastic cells strongly expressed wide-spectrum keratin (polyclonal; DAKO, Copenhagen, Denmark) (Figure 2a) and vimentin (DAKO) (Figure 2b). They also expressed cytokeratin, CAM5.2 (Ventana, Tucson, Arizona, USA), cytokeratin, MNF116 (DAKO) and vascular endothelial growth factor (Santa Cruz Biotechnology Inc, Santa Cruz, California, USA) (Figure 2c). However, they did not consistently express cytokeratins (34βE12, AE1/AE3), epithelial antigen (Ber-EP4), epithelial membrane antigen, myosin, α-smooth muscle, skeletal muscle actin, S-100 protein, desmin, myoglobin, Epstein-Barr Virus (EBNA2, LMP1) or CD10 (CALLA). A few neoplastic cells expressed granulocyte colony stimulating factor (Oncogene Research Products, Boston, Massachusetts, USA) (Figure 3) in their cytoplasm.

Discussion

Atypical spindle cells were present in a myxoid stroma and had proliferated in a sarcomatous pattern. Atypical mitotic figures were frequent. The tumour was compatible with spindle cell sarcoma. The neoplastic cells expressed keratin, cytokeratin, vimentin and granulocyte colony stimulating factor. Therefore, we diagnosed a granulocyte colony stimulating factor producing spindle cell carcinoma.

Spindle cell carcinomas are of two types: monophasic and biphasic. Monophasic spindle cell carcinomas lack classic carcinomatous components. They also lack epithelial foci at the light microscopic level, but ultrastructural and immunohistochemical studies support the concise diagnoses, and all tumours are basically epithelial neoplasms.[3] On the other hand, biphasic spindle cell carcinomas are referred to as squamous cell carcinomas with spindle cell components and are compatible with carcinosarcomas. Additional studies are required to confirm their precise diagnoses, and spindle cells show positivity for cytokeratin.[2] Torenbeek *et al.*[4] have analysed the comparative genomic hybridization of epithelial and spindle cell components in spindle cell carcinomas and carcinosarcomas, using a microdissection method, and found a large overlap of chromosomal aberrations in these two tumours, strongly suggesting a monoclonal origin for both.

Table I summarises those cases of spindle cell carcinoma or carcinosarcoma arising in the pharynx, for which concise

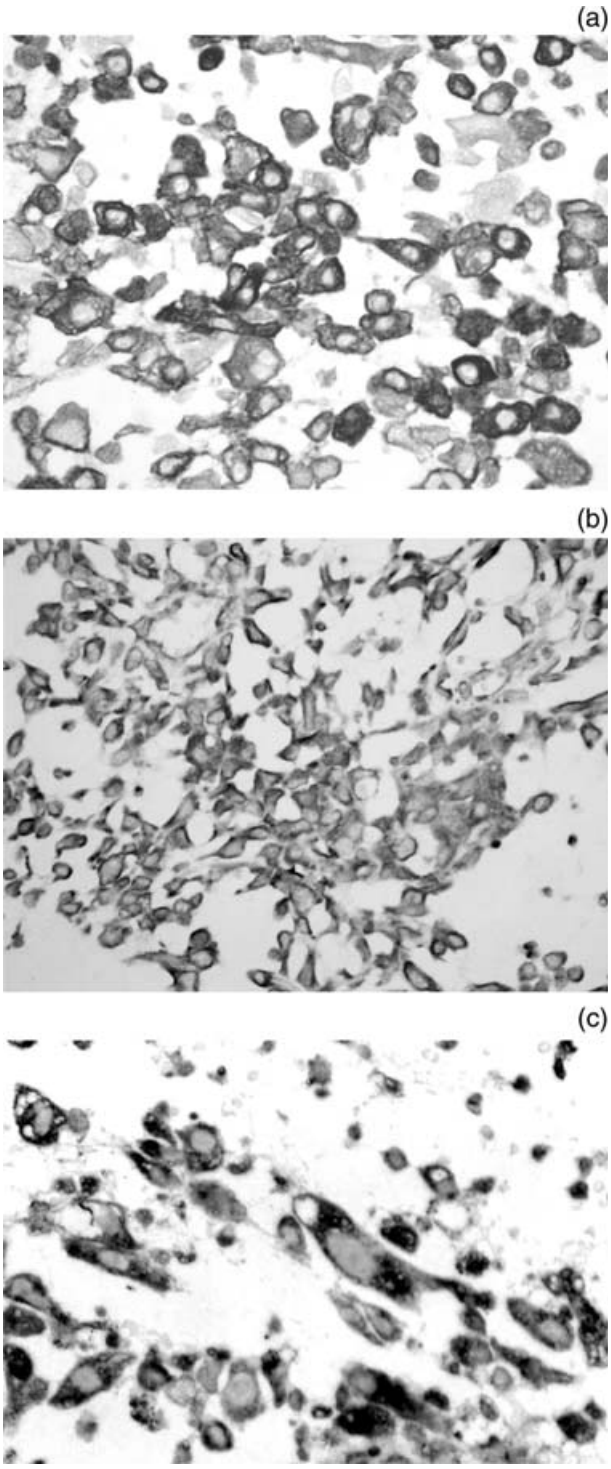

FIG. 2

The neoplastic cells strongly expressed (a) wide-spectrum keratin, (b) vimentin and (c) vascular endothelial growth factor (Immunostain; ×400).

pathological findings were reported.[4–9] Four cases of monophasic spindle cell carcinoma (cases one, six, seven and nine in Table I) were described. Nofal[7] reported the case of a 79-year-old woman with nasopharyngeal carcinoma that showed desmosomes between neoplastic spindle cells. Zarbo *et al.*[9] documented two cases of monophasic spindle cell carcinomas: one expressed only vimentin and had macula adherens at the ultrastructural level,

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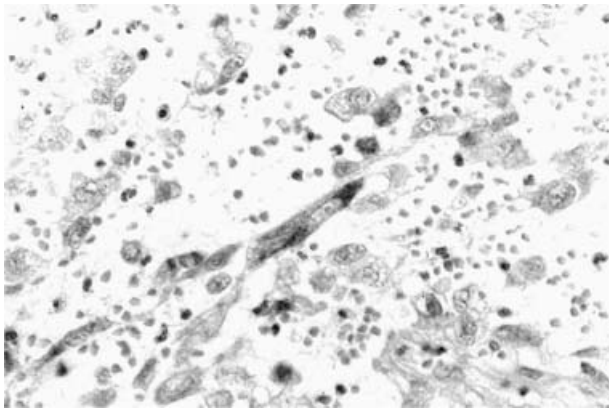

FIG. 3

A few neoplastic cells expressed granulocyte colony stimulating factor (Immunostain; ×400).

while the other showed coexpression of cytokeratin and vimentin and had desmosomes. Takata *et al.*[8] reported the case of a 50-year-old man with a gingival squamous cell carcinoma treated with radiotherapy and surgical therapy 18 years earlier. A spindle cell squamous cell carcinoma developed in the oropharynx and was treated with radical surgical excision and chemotherapy. The tumour showed coexpression of cytokeratin and vimentin.

Many of the cases listed in Table I were treated with radical surgical excision or simple excision. In contrast, the present case was treated with incisional biopsy. Therefore, this biopsy might have made it difficult to rule out the presence of epithelial components within the tumour.

We noted that Olsen *et al.*[10] reported two cases of monophasic spindle cell carcinoma and seven cases of biphasic tumour in the pharynx. Ansari-Lari *et al.*[11] also described five cases of pharyngeal biphasic sarcomatoid carcinoma, and Friedel *et al.*[12] reported six cases of pharyngeal pseudosarcoma. However, these three reports included no summaries of morphological features, immunostaining or ultrastructural findings. Therefore, we omitted these cases from Table I.

Table I shows that 11 of 13 cases expressed several keratins, and 11 of 12 cases expressed vimentin. The remaining two cases (cases three and six) did not express keratins but did express vimentin, and at the ultrastructural level showed desmosomes, tonofilaments or macula adherens. Therefore, we considered various kinds of anti-keratin antibodies and ultrastructural methods to be valuable tools for determining epithelial markers.

The diagnostic criteria for granulocyte colony stimulating factor producing cancers are as follows: (1) prominent granulocytosis without any other evidence of infection; (2) high serum granulocyte colony stimulating factor titre; (3) a decrease in WBC count and a normal serum granulocyte colony stimulating factor titre after tumour resection; and (4) the demonstration of granulocyte colony stimulating factor activity in tumour specimens or tumour cell culture.[13]

Therefore, in the present case, the marked granulocytosis, high serum granulocyte colony stimulating factor level, decrease in WBC count during therapy and expression of granulocyte colony stimulating factor by neoplastic cells were compatible with a granulocyte colony stimulating factor producing cancer.

Matsuo *et al.*[14] reported a case of poorly differentiated squamous cell carcinoma in the buccal mucosa, with a high WBC count, and established a new human carcinoma cell line. Ishigami *et al.*[15] reported a case of poorly

TABLE I

CASES OF SPINDLE CELL CARCINOMA OR CARCINOSARCOMA ARISING FROM THE PHARYNX*

Case	Age (year)/sex	Tumour location	PD	Type	Immunohistochemistry					EM	Outcome	Follow	Ref
					AE1/3	WSK	CAM5.2	Vim	Other				
1	79/F	Nasopharynx	SpCC	Mono						D			7
2	61/M	Pyriform sinus	SpCC	Bi	+		+	+		D, TF	Alive	14 mo	9
3	62/M	Pharynx	SpCC	Bi	−		−	+		D, TF			9
4	58/M	Pyriform sinus	SpCC	Bi	+		+			D, TF	Died	10 mo	9
5	59/M	Pyriform sinus	SpCC	Bi	+		+	+			Alive	3 mo	9
6	72/M	Pyriform sinus	SpCC	Mono	−		−	+		MA	Alive	15 mo	9
7	53/F	Hypopharynx	SpCC	Mono	+		+	+		D			9
8	62/F	Pharynx	SpCC	Bi	+	+		−					5
9	50/M	Oropharynx	SpCC	Mono		−		+	KL1(+)PKK1(+)	D, TF	Alive	96 mo	8
10	42/M	Oropharynx	CS	Bi		+		+			Alive	26 mo	6
11	70/M	Oropharynx	CS	Bi		+		+			Alive	60 mo	6
12		Nasopharynx	CS	Bi	+		+	+					4
13		Epiglottic vallecula	CS	Bi	+		+	+					4
14	67/M	Pharynx	SpCC	Mono		+	+	+	MNF116(+)		Died	4 mo	Present case†

*Cases reported with concise pathological findings. †Tumour produced granulocyte colony stimulating factor. PD = pathological diagnosis; AE1/3 = cytokeratin (AE1/AE3); WSK = wide-spectrum keratin; CAM5.2 = cytokeratin (CAM5.2); Vim = vimentin; EM = electron microscopy; ref = reference; F = female; M = male; SpCC = spindle cell carcinoma; CS = carcinosarcoma; Mono = monophasic; Bi = biphasic; D = desmosomes; TF = tonofilaments; MA = macula adherens; mo = month

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differentiated squamous cell carcinoma in the gingiva which showed marked granulocytosis and positive staining of cancer cells for granulocyte colony stimulating factor. Therefore, previously reported cases and the present case confirm that head and neck cancers producing granulocyte colony stimulating factor are poorly differentiated carcinomas. In addition, the present report may be the first to document a granulocyte colony stimulating factor producing cancer arising in the pharynx.

- **This paper describes a 67-year-old man with a left pharyngeal tumour whose peripheral blood showed granulocytosis**
- **The tumour was diagnosed as a granulocyte colony stimulating factor producing, monophasic spindle cell carcinoma**
- **The patient died four months after the initial symptoms appeared**

Although granulocyte colony stimulating factor promotes angiogenesis, the exact mechanism is not known. The relationship between granulocyte colony stimulating factor, granulocyte colony stimulating factor receptor and vascular endothelial growth factor is also unclear. Ohki *et al.*[16] have shown that granulocyte colony stimulating factor modulates angiogenesis by increasing both neutrophil numbers and their release of vascular endothelial growth factor. Tsuzuki *et al.*[17] have reported a lack of association between granulocyte colony stimulating factor receptor expression and granulocyte colony stimulating factor staining. These authors have also reported that granulocyte colony stimulating factor receptor positive groups have a significantly worse prognosis than do granulocyte colony stimulating factor receptor negative groups, but that granulocyte colony stimulating factor production does not appear to influence survival.

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