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Undifferentiated carcinoma of the nasopharynx and leukemoid reaction: report of case with literature review

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Abstract
A case of undifferentiated carcinoma of the nasopharynx presenting as a cervical mass associated with a paraneoplastic neutrophilic leukemoid reaction is reported. The diagnosis of undifferentiated nasopharyngeal carcinoma of the Regaud type was established by the presence of aggregates of epithelial neoplastic cells separated by areas of reactive lymphoid cells; the epithelial nature being confirmed by the positivity for epithelial markers (AE1/AE3, EMA). Serum IL-1α, GM-CSF and TNFα remained undetectable suggesting that these factors were not involved in the occurrence of the paraneoplastic leukemoid syndrome.

Key words: Nasopharyngeal neoplasms; Carcinoma; Paraneoplastic syndromes; Leukemoid reaction

Introduction

Undifferentiated carcinoma of nasopharyngeal type (UCNT) is an epidermoid-lineage cancer which is characterized by two kinds of histological patterns. The first one-so-called Regaud's type displays well-defined epithelial nests separated by broad areas of inflammatory reaction (Regaud and Reverchon, 1921). The second one designed as Schmincke's type is characterized by tumour cells growing in a diffuse fashion mimicking malignant lymphoma. It has been established as a specific clinical entity from other head and neck squamous cell carcinomas (Cvitkovic *et al.*, 1993). The main epidemiological and clinical aspects that differentiate UCNT from other head and neck tumours are the absence of correlation with tobacco or alcohol consumption, the sex ratio (3/1, male/female) and the adolescence/early adulthood peak of frequency (Ho, 1971). UCNT is rare in most parts of the world but its rate is high in Southeast Asia and lower, but still elevated, in North and East Africa (Henle and Henle, 1981). The classical treatment is by external-beam irradiation. If tumours at early stages are curable with radiotherapy, advanced stage lesions have a very poor prognosis (15 per cent to 45 per cent five-year survival rate) caused by metastatic spread (Huang *et al.*, 1985; Bailet *et al.*, 1992). Several paraneoplastic syndromes have been described in association with UCNT: the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (Kavanagh *et al.*, 1992), hypertrophic osteoarthropathy (Pierre-Marie syndrome) (Zornoza *et al.*, 1977; Maalej *et al.*, 1985), tumour-specific associated fever and leukemoid reactions (Cvitkovic *et al.*, 1993). It was hypothesised that the latter could be related to interleukin-1 alpha (IL-1α) secretion by the epithelial cells and/or by reactive lymphocytes infiltrating the tumoral cells (Busson *et al.*, 1987; Cvitkovic *et al.*, 1993). To date, this hypothesis has not been supported by direct measurements of IL-1α and the exact pathogenesis of the paraneoplastic leukemoid reaction remained largely unknown.

We thus measured IL-1α, granulocyte monocyte colony-stimulating factor (GM-CSF) and tumour necrosis factor (TNFα) plasma levels in a patient with a leukemoid reaction associated with an undifferentiated carcinoma of the nasopharyngeal type with cervical metastasis.

Case report

A 24-year-old North-African male patient was admitted to the ENT department of Brugmann University Hospital with a painless mass in the left cervical region that had gradually enlarged for two months and was associated with fever and trismus. His past medical history revealed no significant disease. Physical examination showed an 8 × 8 × 11 cm left cervical mass (Figure 1) associated with an enlarged left tonsil. A nasal endoscopy disclosed erosion of the left wall of the nasopharynx. Computerized tomography of the head and neck confirmed the destruction of the lateral wall of the nasopharynx by a tumoral process corresponding to node involvement that was in continuity with the tonsil and the cervical mass (Figures 2 and 3). Biopsies of the nasopharynx and the cervical mass revealed an undifferentiated carcinoma of the nasopharynx. There was no lung, bone nor liver metastasis. The spleen was not enlarged. Initial blood laboratory data were as follows: leukocyte count: 80,900 elements/μl (normal level (NL): 4,500–10,500) (neutrophils 70 per cent, eosinophils one per cent, monocytes 11 per cent, lymphocytes 16 per cent), c-reactive protein (CRP): 8.8 mg/dl (NL: <0.5 mg/dl), erythrocyte sedimentation rate (ESR): 32 mm/first hour (NL: 0–10 mm/first hour), haemoglobin (Hb): 11.8 g/dl (NL: 14–18 G/dl), platelets: 429,000 elements/mcl (NL: 140,000–440,000 elements/μl); serum sodium: 135 mEq/l (NL: 135–143 mEq/l, serum potassium; 3.5 mEq/l

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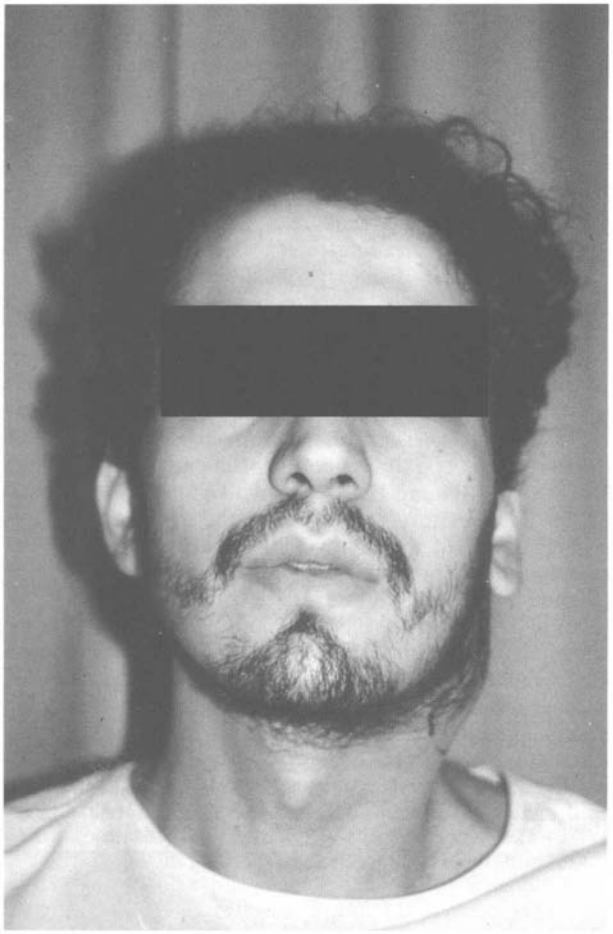

FIG. 1
Presenting features of the cervical mass.

(NL: 3.5–4.8 mEq/l), serum chloride: 95 mEq/l (NL: 95–107 mEq/l, total serum calcium; 9.6 mg/dl (NL: 9.1–10.2 mg/dl), serum phosphate: 2.5 mg/dl (2.4–4.4 mg/dl). Concurrently the leukocyte count and the volume of the cervical metastasis of UCNT increased whereas CRP and ESR remained only slightly increased (Table I). Focal or systemic signs or symptoms of infection or inflammation were lacking. This evolution illustrated the paraneoplastic character of this leukemoid reaction. Epstein-Barr virus (EBV) serology was negative.Using standard methods of ELISA (Medgenix, Fleurus, Belgium), no detectable serum levels of GM-CSF, IL1α and TNFα could be measured throughout the course of the disease. The diagnosis of undifferentiated carcinoma of the nasopharynx associated with cervical metastasis and paraneoplastic leukemoid reaction was established and chemotherapy (cisplatin 100 mg/m^2 of body surface (BD) and 5 FU 1000 mg/m^2 of BD) with adjuvant radiotherapy were administered.

Pathological findings

Macroscopically, the specimen consisted of two small fragments of nasopharyngeal tissue and two others of cervical metastasis. Routinely processed and stained tumour tissue from the specimen was used for light microscopy. Sections showed relatively well-defined aggregates of epithelial neoplastic cells separated by areas of reactive lymphoid cells (Figure 4). Immunohistochemistry was performed on paraffin sections using a supersensitive detection kit (Biogenex).

Antibodies against cytokeratin (including CAM 5.2 and a AE1/AE3 cocktail), EAM, CEA and LCA were used. The epithelial cells were positive for the AE1/AE3 cocktail (Figure 5) as well as for EMA. They were negative for the cytokeratin CAM 5.2 and for CEA; the former having been repeated twice. The LCA stained the lymphoid cells. A diagnosis of undifferentiated nasopharyngeal carcinoma of the Regaud type was thus given.

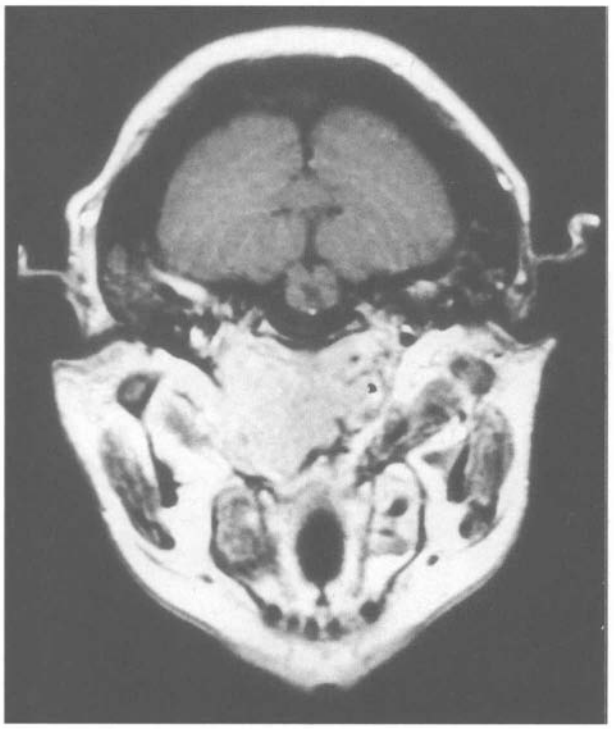

FIG. 2
CT scan (L) nasopharynx region.

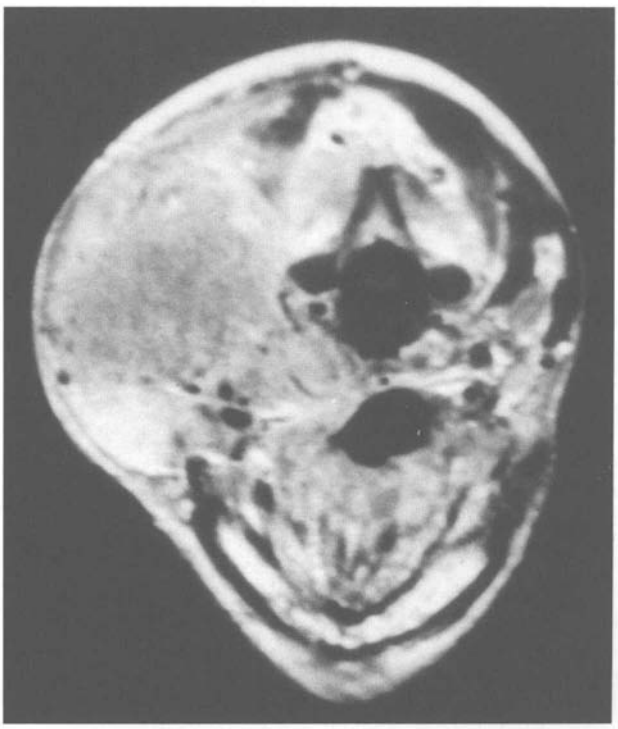

FIG. 3
CT scan (L) cervical region.

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TABLE I
INITIAL LABORATORY DATA (BLOOD)

	J1	J10	J25 Chimio	J40
Tumour volume (cm^3)	700	1300	—	—
Leukocyte count (e/μl)	80,900	90,270	155,000	9,000
Neutrophilia (%)	70	88	90	89
CRP (mg/dl)	8.8	5	2.8	0.5
GM-CSF (pg/ml)	<15	<15	<15	<15
IL-1-alpha (pg/ml)	<15	<15	<15	<15
TNF-alpha (pg/ml)	<15	<15	<15	<15

GM-CSF, IL-1-alpha, TNF-alpha≤15 pg/ml = not significant.

Discussion

Several paraneoplastic syndromes have been associated with UCNT: hyponatraemia due to SIADH (Kavanagh *et al.*, 1992), hypertrophic osteoarthropathy (Zornoza *et al.*, 1977), fever of unknown origin and leukemoid reaction (Cvitkovic *et al*, 1993). The leukemoid reaction is defined by the elevation of the peripheral white blood cell count (>2000/μl) in absence of infection or leukaemia. Cvitkovic *et al.* have described two new clinical symptoms associated with the UCNT: tumour-specific associated fever and neutrophilic leukemoid reaction. They have observed a 16 per cent rate of leukemoid reaction in UCNT. The paraneoplastic origin of these phenomena suggested taking into account the absence of infection and/or tumour necrosis. In addition, the lack of relationship between the leukemoid reaction and the tumoral mass also favoured the hypothesis of a dysregulation of the immune response. GM-CSF, TNFα and IL-1α are involved in the generation of the inflammatory response and the synthesis and the differentiation of the neutrophilic leukocyte. IL-1α is an essential mediator of the inflammatory immune response (Billaud *et al.*, 1989) and IL-1α directly produced by tumoral cells of a thyroid squamous carcinoma has been reported to be responsible for paraneoplastic fever and hyperleucocytosis (Sato *et al.*, 1987). In UCNT, different immunoregulatory molecules produced and released by the malignant epithelial cells could attract and locally stimulate T cells to produce cytokines. In addition, IL-1α has been demonstrated to be secreted by tumoral UCNT epithelial cells. Increased serum levels of IL-1α has been

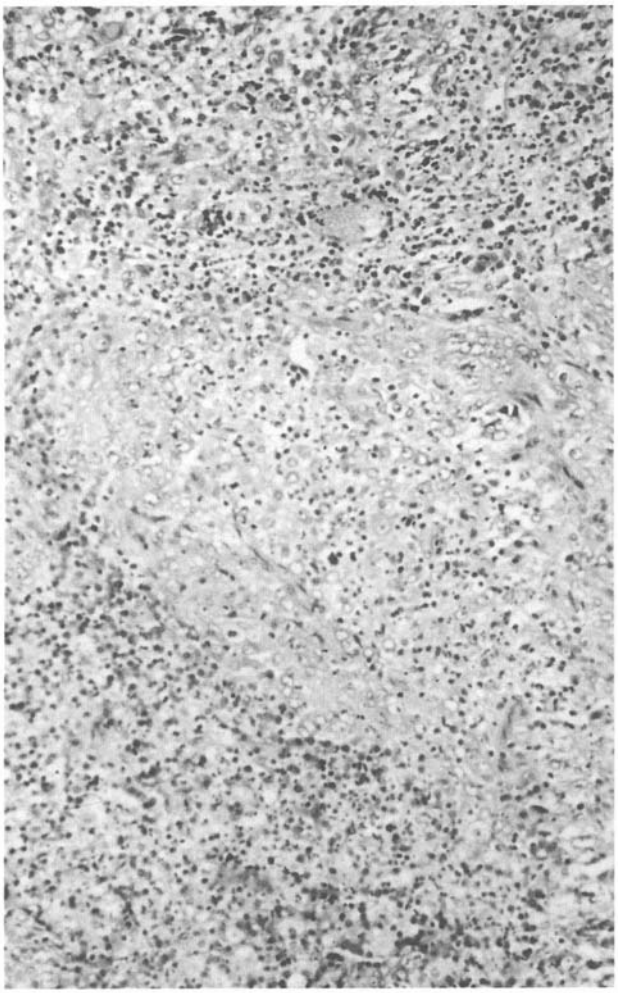

FIG. 4
Histological appearance of undifferentiated carcinoma of the nasopharynx (H & E; ×400).

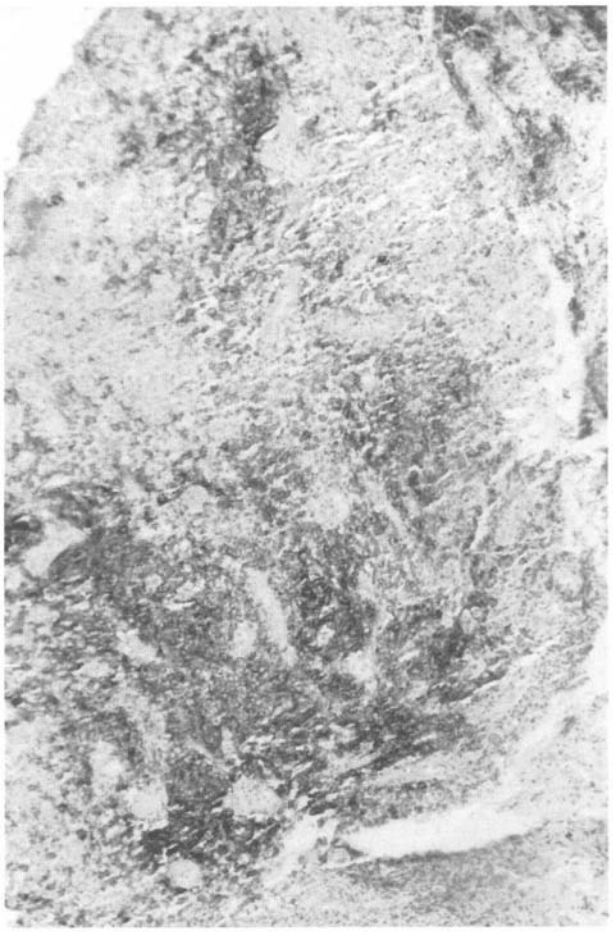

FIG. 5
Epithelial tumour cells of UCNT show immunoreactivity for AE1/AE3 cytokeratin cocktail (Phosphatase Alkaline New Fuschin; ×400).

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hypothesized to be responsible for the leukemoid reaction in UCNT. This hypothesis is not confirmed by our data. Indeed, in the present case, IL-1α remained undetectable in serum throughout the study. Moreover, neither GM-CSF nor TNFα were found to be increased. The dissociation between the marked neutrophilia and serum levels of c-reactive protein provides no evidence for a role of IL-1α in the present case. Indeed IL-1α is a potent stimulant of c-reactive protein synthesis in inflammatory disorders. As GM-CSF, TNFα and IL-1α remained undetectable, we have demonstrated in this case that these cytokines were not involved in the occurrence of the paraneoplastic leukemoid reaction. The absence of stimulation of other blood cell lineages favours the hypothesis that other factors (such as granulocyte-colony stimulating factor (G-CSF) which stimulates later blood cell differentiation) could be involved in the pathogenesis of the paraneoplastic leukemoid reaction.

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