Breast carcinoma metastases in paranasal sinuses, a rare occurrence mimicking a primary nasal malignancy. Case report

Carcinoma mammario metastatizzato ai seni paranasali. Un raro evento che mimava un tumore maligno primitivo nasale

D. MARCHIONI, D. MONZANI, G. ROSSI*, F. RIVASI*, L. PRESUTTI
Department of Otorhinolaryngology, and Department of Pathologic Anatomy and Forensic Medicine;
* Section of Pathology, University of Modena and Reggio Emilia, Modena, Italy

Key words

Paranasal sinuses • Metastasis • Breast carcinoma • Immunohistochemistry • Prognosis

Parole chiave

Seni paranasali • Metastasi • Carcinoma mammario • Immunoistochimica • Prognosi

Summary

Metastatic tumours to the paranasal sinuses are an exceedingly rare event, the large majority being of renal origin. Herein, a case of metastatic breast carcinoma to the right maxilla is described which occurred 4 years after radical mastectomy, clinically and radiologically presenting as a primary sinonasal mass. Only the histopathologic examination together with a broad spectrum of immunohistochemical antibodies were useful in confirming the origin of the neoplasm.

Riassunto

Il ritrovamento di lesioni metastatiche a livello dei seni paranasali è un evento estremamente raro, queste lesioni in prevalenza sono di origine renale. Lo studio da noi proposto presenta un caso di carcinoma della mammella metastatizzato nel mascellare di destra comparso a 4 anni dalla mastectomia radicale e che i test clinici e radiologici hanno evidenziato come una massa primitiva nasosinusale. Soltanto l'esame istopatologico congiuntamente ad un ampio spettro di anticorpi immunoistochimici ha contribuito a confermare l'origine della neoplasia.

Tumours metastasizing from distant organs to the head and neck region are uncommon, but those involving the nasal cavity and paranasal sinuses are exceedingly rare. To our knowledge, <100 cases of metastatic carcinoma (ca) to the paranasal sinuses have been reported in the literature. The origin of metastatic tumours, in this anatomic site, is often from renal cancer [1 2], whereas only few reports have described sinonasal metastatic tumours from the breast, gastrointestinal tract, genitourinary tract and lower respiratory tract [2]. The symptoms of metastatic ca to the paranasal sinuses are usually not specific. Generally, the initial symptoms are facial pain, epistaxis and nasal obstruction [2 3] and the latent period from the initial primary malignancy to sinonasal metastasis varies considerably. The mechanism of metastasis to the paranasal sinuses is unclear, although it is likely that breast ca spreads both by way of blood vessels and lymphatic channels [4]. Diagnosis is often difficult and patients are initially treated with antibiotics for clinically suspected infective sinusitis, without any result. It is well known that breast ca develops metastases in >50% of cases, but the occurrence of a metastatic breast ca to the head and neck is very rare [2-5]. However, it has been reported that breast cancer may involve various sites of the head and neck region, including larynx [6], temporal bone [7], nasopharynx [8], parotid gland [9], nose and paranasal sinuses [2].

The present report deals with a case of breast cancer metastastic to the right maxilla originally suspected to be a primary malignancy, and underlines how the final diagnosis clearly requires a meticulous clinicopathological analysis. A review of the literature, appears to indicate that, once it occurs, metastatic breast ca to the sinonasal region may be related to an extremely poor prognosis. Finally, use of a broad spectrum of an appropriate panel of immunohistochemical markers may play a key role in this specific setting.

Case report

In November 1995, a 78-year-old female was diagnosed as having a grade 3, infiltrating ductal ca of the

right breast. Right radical mastectomy with axillary regional lymph node dissection was performed. After surgery, the patient underwent chemotherapy. The patient's medical history was significant for type II diabetes and hypertension. In December 2001, the patient experienced a right-sided non-specific headache. No previous history of nasal obstruction or epistaxis was documented. Three weeks later, a right periorbital mass, causing diplopia and ptosis with palsy of the right III nerve with medial rectus muscle involvement, was clinically noted. Laboratory tests showed moderate anaemia with a white blood count (WBC) of 10,500 (per mm^3) consisting of 83.4% neutrophils. Chest X-ray did not reveal pulmonary lesions. At clinical examination, anterior rhinoscopy showed moderate oedema of the right middle meatus with no signs of inflammation. Posterior rhinoscopy revealed normal respiratory mucosa. Cervical lymphadenopathy was not found.

A computed tomography-scan of brain and paranasal sinuses showed a mass characterized by soft tissue densities occupying the right maxilla and the ethmoid sinuses with evidence of bone erosion. The lamina papyracea was interrupted, while the recti medial muscles and the right optic nerve were intact. Magnetic resonance imaging (MRI) of brain and paranasal sinuses revealed a soft tissue mass occupying the right maxilla and ethmoidal air spaces, extending to the right frontal sinus and into the orbit with a padded periorbital tissue (Fig. 1). The skull base was not involved. The periosteum of the entire medial wall of the orbit, from the roof to the floor, was thickened. Brain tissue showed normal signal intensity. Endoscopic ethmoidectomy and maxillary antrostomy, together with several biopsies, culture specimens and antral lavage, were performed. The sinonasal biopsies consisted of different sized fragments, diameter ranging from 2 to 3.5 cm, with a polypoid appearance. The specimens were fixed in 10% buffered-formalin and then routinely paraffin-embedded. Slices, 4µ thick, obtained from the relevant blocks were stained with haematoxylin and eosin (H&E). For immunohistochemical analysis, 3µ thick sections were obtained from a representative block. Sections were air-dried overnight at 37°C, then deparaffined in xylene and rehydrated through a decreasing concentration of alcohol to water. Endogenous peroxidase activity was blocked by immersion for 10 minutes in 3% hydrogen peroxidase (H_2O_2) in methanol. The following antibodies were applied: oestrogen receptors (clone 1A6, Dako, Glostrup, Denmark; 1:125 dilution), progesterone receptors (clone 1D5, Dako; 1:100 dilution), Ki-67 (clone Mib-1, BioOptica, Milan, Italy; 1:100 dilution), p53 (clone DO-7, NeoMarkers, San Josè, CA, USA; 1:200 dilution), c-erb-B2 (clone CB11, Novocastra, Newcastle upon Tyne, UK; 1:100 dilution),

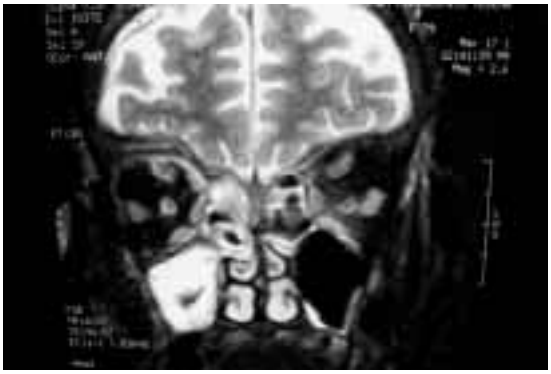

Fig. 1. Magnetic resonance imaging of paranasal sinus showing soft tissue mass occupying right maxilla and ethmoid air spaces, and extending to right frontal sinus.

GCDFP-15 (clone 23A3, Novocastra; 1:50 dilution), and cytokeratins (clone MNF116, Dako; 1:200 dilution). A microwave antigen retrieval was performed, for all antibodies, for 30 minutes in 0.01 mol/L citrate buffer (pH 6.0). Incubation with the primary antibodies was accomplished with a modified avidin-biotin peroxidase technique using a commercial automated immunostainer (Ventana, Strasbourg, France); 3'-3-diaminobenzidine was used as the chromogen and Harris haematoxylin as the counterstain. Suitable positive control tissues were included to confirm antibody specificity. Negative controls were included in each test by substituting the primary antibodies with non-immune mouse IgG. For oestrogen and progesterone receptors, p53, and Ki-67, the nuclear staining was evaluated, in a quantitative way, as the percentage of positive neoplastic cells on the entire tumour. For c-erb-B2, and GCDFP and cytokeratin, respectively, the membrane and cytoplasmic staining intensity were recorded using a 0 to 3+ scale (0, negative; 1+, weak; 2+, moderate; 3+, strong). Upon histological examination, the tissue presented as a polypoid lesion. The overlying respiratory epithelium was normal, while diffuse infiltration by a poorly-differentiated ca was noted in the subepithelial stromal tissue (Fig. 2). The neoplastic cells consisted of round to polygonal elements with ample eosinophilic cytoplasm and small nucleoli (Fig. 3). These were arranged in solid nests with centrolobular necrotic foci, lacking tubular or glandular architecture, and displaying several mitotic figures. The tumour also showed diffuse involvement of the stromal vessels and bone thin lamellae. At immunohistochemistry, the tumour cells did not react with the oestrogen and progesterone receptors, or with c-erbB-2, whereas a strong immunostaining was found for cytokeratins (Fig. 4). A weak to moderate immunostaining for GCDFP-15 was noted. The tumour

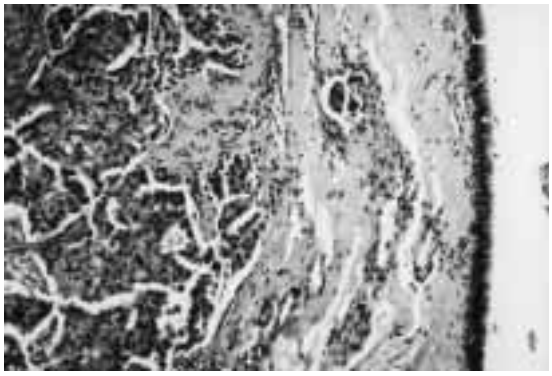

Fig. 2. Microphotograph showing ethmoid sinus mucosa with infiltration of ductal breast carcinoma (H&E, orig. magn. X 40).

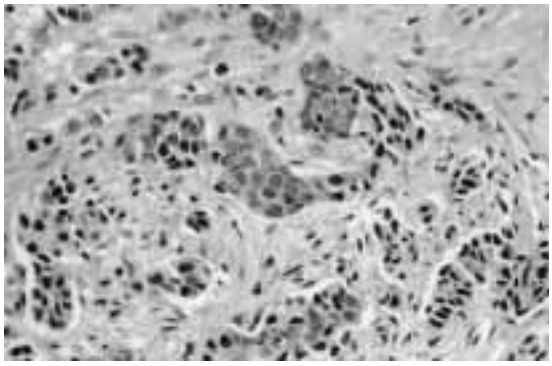

Fig. 3. Tumour cells show poorly-differentiated carcinoma (H&E, orig. magn. X 200).

showed a high Labelling Index (LI) by Ki-67 (35%) and p-53 nuclear overexpression (75%). Archival tissue from the previous breast carcinoma (grade 3, infiltrating ductal ca with axillary lymph node metastases) were then retrieved for histological and immuno-histochemical comparison. The primary breast ca showed the same histological and immunophenotypic characteristics as the sino-nasal carcinoma. At this point, a diagnosis of metastatic breast ductal ca to the sino-nasal tract was favoured.

The patient was referred back to the Oncology Unit for local radiotherapy to the right maxilla. During follow-up, no new local relapse was observed. Nasal cavity endoscopy performed two months after surgery revealed oedema of the middle meatus without signs of disease relapse. After four months, the patient died of respiratory failure due to multiple pulmonary metastases.

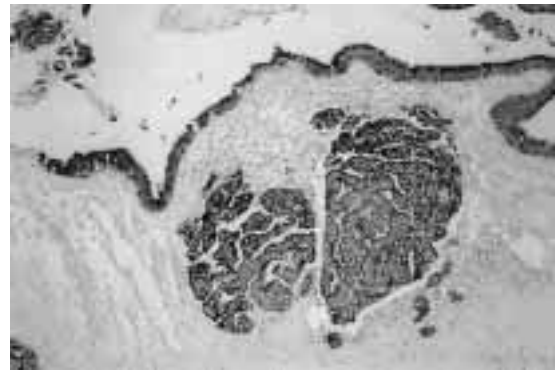

Fig. 4. Neoplastic cells diffusely involve vascular channels of subepithelial stromal tissue (H&E orig. magn. X 100).

Comment

As reported in the epidemiological studies of Friedmann and Osborne [10] and Mochimatsu et al. [11] metastatic tumours involving the head and neck region are very uncommon, whilst metastatic diseases occurring in the nose and paranasal sinuses are exceedingly rare. Metastases, in this area, are often secondary to renal cancer, as reported by Bernstein et al. [2] in studies on 82 patients with metastatic disease involving the paranasal sinuses and revealed that the large majority of metastases derived from renal ca (40 patients) followed by testicular tumours, bronchial cancer, gastrointestinal neoplasm and breast cancer [2]. Of note, only one case of metastatic melanoma to the ethmoid sinus has been reported in the literature [12].

Signs and symptoms related to the occurrence of a metastatic tumour in the sinonasal tract are non-specific and may remain silent for a long time. Furthermore, in some cases, the first symptoms may result from nasal metastasis before a diagnosis of the primary tumor is made [13]. While metastatic tumours to the paranasal sinuses have no distinctive clinical features by which to make early diagnosis, facial pain, epistaxis, nasal obstruction and facial asymmetry represent the main manifestations [2-5]. These symptoms are similar to those seen in the course of upper respiratory tract infections. Conversely, diplopia, epiphora, blepharoptosis, decreased visual acuity and proptosis are the main clinical symptoms when the metastatic tumour develops in the orbit [13 14], while headache might be attributed to meningeal involvement from metastatic carcinoma [13]. The possibility of a primary or metastatic maxillary tumour should be suspected when treatment of a sinus infection is not effective. Given the high content of intratumoural vessels and the particular angiotrophism of renal ca, metastatic

tumours originating from the kidney are usually haemorrhagic. In fact, epistaxis is present in >70% of these tumours metastatic to the paranasal sinuses [2-15]. According to Yoshimura et al. [16], metastasis from renal cancer should be strongly suspected in patients with a medical history of renal ca associated with epistaxis. In some cases, since the final diagnosis is based mainly on histopathological findings, a biopsy of the sinuses is clearly indicated. Conversely, CT-scan and MRI may be very helpful in defining the tumour site, extent, and involvement of soft tissue structures. As in our case, metastatic tumours originating from the breast are not haemorrhagic, and facial pain and asymmetry are the most common initial symptoms. This is supported by the results of previous investigations in which metastatic breast cancer to the antral wall was reported [2 17-21]. However, metastatic breast cancer has been observed in other sites of the paranasal sinuses, including sphenoid [13 21], frontal sinus [22 23], and ethmoid [3 5 24 25]. Austin et al. [24] first reported a case of breast cancer originally found as a microscopic metastatic focus in the vascular channels of the paranasal sinuses. In 2001, Monserez et al. [5] reported another case of breast metastasis manifesting as bilateral symmetric expanding masses in the ethmoidal sinuses.

In the literature, the interval between the diagnosis of breast ca and paranasal metastasis has been reported to range from 3 months to 12 years and the mechanism of metastasis to the paranasal sinuses is unclear. Nahum and Bailey [20] emphasized the role of the vertebral venous plexus in tumour spread, this system consisting of prevertebral and epidural veins with innumerable intertwining vessels that communicate, at every level, with the intercostal veins, venae cavae, azygous vein and pelvic system. On the contrary, Monserez et al. [5] suggested that ethmoidal involvement by metastatic ca might be due to direct transcribrosal spread.

The choice of appropriate treatment, in such cases, is extremely difficult since the surgical approach cannot be radical, surgery usually being limited to obtaining a tumour biopsy for differential diagnosis. The vast majority of these patients undergo palliative radiotherapy in combination with chemotherapy. It is noteworthy that, once breast carcinoma has metastasised to the sinonasal tract, this finding should be considered a bad prognostic parameter. In fact, a review of the literature showed that all those patients presenting this finding died some months after diagnosis. From a pathologic point of view, diagnosis may often be difficult if based only on morphologic data. Breast ca metastasising to the paranasal sinuses can mimic a primary ca of the nasal cavity, both tumours sharing an epithelial differentiation. However, the latter commonly shows neoplastic changes in the overlying respiratory epithelium and does not display positive immunostaining for oestrogen or progesterone receptors and GCDFP-15, a specific marker of mammary origin. A meticulous search in the patient's pathologic medical history and close collaboration between physician and pathologist remain the most useful tools in discriminating between a primary versus a secondary tumour.

References

1 Saitoh H. *Distant metastasis of renal adenocarcinoma*. Cancer 1981;48:1487-91.

2 Bernstein JM, Montgomery MD, Balogh K Jr. *Metastatic tumours to maxilla, nose, and paranasal sinuses*. Laryngoscope 1966;76:621-50.

3 Nelson EG, Goldman ME, Hemmati M. *Metastatic carcinoma of the ethmoid sinus.* Otolaryngol Head Neck Surg 1990;103:120-3.

4 Batson OV. *The function of the vertebral veins and their role in the spread of metastasis*. Ann Surg 1988;112:138-49.

5 Monserez D, Vlaminck S, Kuhweide R, Casselman J. *Symmetrical ethmoidal metastases from ductal carcinoma of the breast, suggesting transcribrosal spread*. Acta Oto-rhinolaryngol 2001;55:251-7.

6 Wanamaker JR, Kraus DH, Eliachar I, Lavertu P. *Manifestations of metastatic breast carcinoma to the head and neck*. Head & Neck 1993;15:257-62.

7 Feinmesser R, Libson Y, Uziely B, Gay I. *Metastatic carcinoma to the temporal bone.* Am J Otolaryngol 1986;7:119-20.

8 Saab GA, Abdul-Karim FW, Samara M. *Breast carcinoma metastatic to the nasopharynx*. J Laryngol Otol 1987;101:723-5.

9 Raut V, Sinnathuray AR, McClean G, Brooker D. *Metastatic breast carcinoma in the parapharyngeal space.* J Laryngol Otol 2001;115:750-2.

10 Friedmann I, Osborne DA. *Metastatic tumours of the ear, nose and throat*. J Laryngol Otol 1965;79:576-91.

11 Mochimatso I, Tsukuda M, Furukawa S, Sawaki S. *Tumours metastasizing to the head and neck - a report of seven cases*. J Laryngol Otol 1993;107:1171-3.

12 Bizon JG, Newman RK. *Metastatic melanoma to ethmoid sinus*. Arch Otol Head Neck Surg 1986:112:664-7.

13 Barrs DM, McDonald TJ, Whisnant JP. *Metastatic tumors to the sphenoid sinus.* Laryngoscope 1979;89:1239-43.

14 Bloch RS, Gartner S. *The incidence of ocular metastatic carcinoma*. Arch Ophthalmol 1971;85:673-5.

15 Johnson ISM, Rani M, Campbell JB. *Renal derived epistaxis*. J Laryngol Otol 1993;107:144-5.

16 Yoshimura T, Suenaga T, Kozaki H, Oohashi N, Sakai N. *A case of renal cell carcinoma revealed by metastasis to the nasal cavity and paranasal sinuses*. Sapporo Hosp Med 1989;49:31-5.

[17] Robin IG. *Malignant disease of the maxilla*. Guy's Hosp Rep 1939;19:301-35.

[18] Garret MJ. *Metastatic tumors of the paranasal sinus simulating primary growths*. J Fac Radiol 1959;10:151-9.

[19] Blake H, Blake F. *Breast carcinoma metastatic to maxilla*. Oral Surg Oral Med Oral Pathol 1960;13:1099-106.

[20] Nahum AM, Bailey BJ. *Malignant tumors metastatic to the paranasal sinuses*. Laryngoscope 1963;73 942-53.

[21] Jortay AM. *Metastatic tumors in oral cavity, pharynx and paranasal sinuses*. Acta Chir Belg 1971;70:715-28.

[22] Archilei G. *Metastatic orbit-paranasale de carcinoma mammario*. Boll Mal Orecch 1959;77:218-24.

[23] Myers EN. *Metastatic carcinoma of the breast occurring in the frontal sinus*. J Laryngol Otol 1968;82:485-7.

[24] Austin JR, Kershiznek MM, McGill D, Austin SG. *Breast carcinoma metastatic to paranasal sinuses.* Head Neck 1995;17:161-5.

[25] Garcia TD, Molina QC, Sanz FR. *Ethmoid metastasis of primary breast tumour*. Acta Otorrinolaringol Esp 1998;49:163-4.

■ Received: November 7, 2003
Accepted: January 13, 2004

■ Address for corespondence: Dr. D. Marchioni, Clinica Otorinolaringoiatrica, Azienda Policlinico, Università di Modena e Reggio Emilia, via del Pozzo 71, 41100 Modena, Italy. Fax +39 059 4224249.
E-mail: marchionidaniele@yahoo.it