CASE REPORT

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About an unique case of embryocarcinoma with nasal onset*

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SUMMARY

Primary extragonadal germ cell tumours (PEGCT) are rare neoplasms with generally poor prognosis, different behavior, and natural course compared to their gonadal counterparts. Both primary and salvage treatment of these tumours constitute a challenge.
Embryocarcinoma (EC) constitutes one of the subtypes of germ cell tumours. Its site of primary onset can either be gonadal or extragonadal, more frequent in infancy and childhood, the sacral and cranial regions being the most affected, while gonadal sites (ovary and testis) are more frequently involved in childhood. The authors observed a case of EC with nasal onset in a young male, never reported before in the literature. The patient underwent 6 courses of chemotherapy and further surgery by means of an endoscopic approach, without post-surgical sequelae. A 5-years follow-up, with periodic controls, laboratory tests and imaging, all without signs of recurrence, confirmed that this unusual location of EC responded exclusively to primary chemotherapy, while earlier studies proved EC being responsive, in other sites of onset, to a combination of chemotherapy, radical surgical excision of the neoplasm, and radiotherapy.

Key words: germ cell tumours, embryocarcinoma, nasal onset, chemotherapy

INTRODUCTION

Normally present in masculine and feminine gonads, where they contribute to the gametogenic activity, totipotential germ cells may give rise to a broad range of tumours. Malignant germ cell tumours are relatively uncommon, accounting for approximately 3 to 5% of all childhood malignancies [1,2]. Primary germ cell tumours also occur in extragonadal sites in the anatomic midline [3,4], representing a rare group of neoplasms histologically identical [5], but with a poor prognosis, different behaviour, and natural course compared to their gonadal counterparts [6]. Extragonadal tumours are more common in neonates and infants, mainly affecting females [7], whereas gonadal sites predominate in childhood and adolescence [1,8].

Many subtypes of primary extragonadal germ cell tumours (PEGCT) exist, including embryocarcinomas, yolk sac tumours, seminomas, choriocarcinomas and teratomas, each of them characterized by specific serologic and immunohistochemical features. Their sites of onset are more frequently mediastinal, central nervous system, sacrococcygeal region and retroperitoneal [4,7,9-15]. In the head and neck region PEGCT account for only 5% of all benign and malignant germ cell tumours [16]. In the literature sporadic cases have been reported, with isolated cervical [17,18], maxillary [19], gingival [20], auricular [21], orbital, maxillofacial and retroauricolar [16] presentations. In the cranial cavity PEGCT have been described in the pinealis gland [14] and in the suprasellar region [7].

The initial treatment of choice for PEGCT is cisplatin-based chemotherapy [6,22] alone or in association with radiotherapy [5,23-26], followed by surgery in cases of residual disease [11,27], or persistent elevated serum markers after first-line chemotherapeutic treatment [28].

Confirmed histology, stage and location of primary tumour and persistence of elevated serum markers following cisplatin-based chemotherapy have shown to represent the most relevant factors for long-term outcome. The 5-year overall survival ranges between 89% for stage I-II seminomatous extragonadal germ-cell tumours (EGCT) and 71% for nonseminomatous ones, the retroperitoneal locations having a better prognosis than the mediastinal ones and the presence of liver, lung or CNS metastases acting as independent adverse factors [29,30].

We have recently observed a case of embryocarcinoma (EC) with nasal onset in a young male, never reported before in the literature. Because of the rarity of the case as well as the success of the treatment adopted, we report it after a 5-years follow-up.

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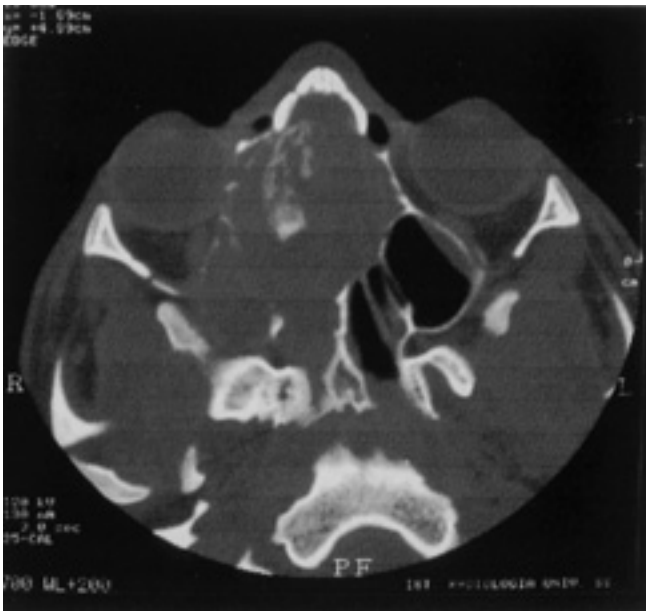

Figure 1. In the axial cut all right paranasal cavities are occupied by a neoplasm with soft tissue CT density.

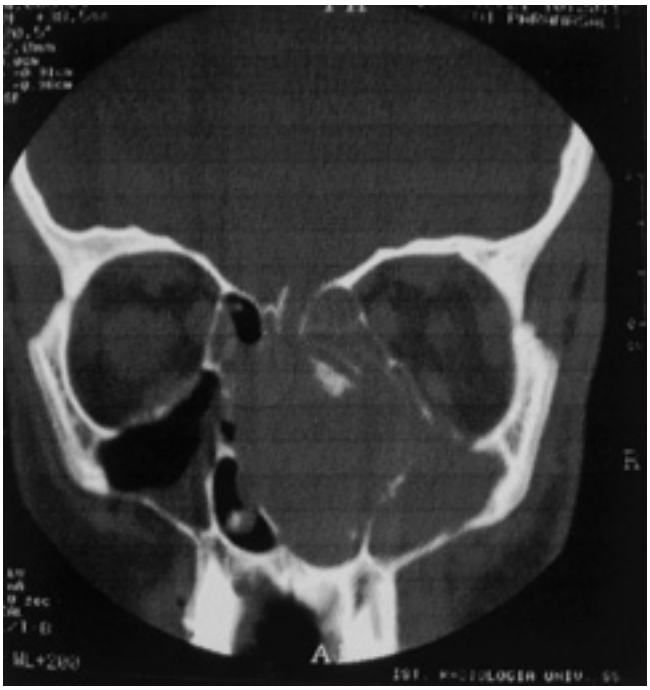

Figure 2. Coronal cut showing the nasal septum, ethmoid cells and medial wall of maxillary sinus displaced by the mass.

CASE REPORT

In June 1998 R.F., a 14-year old Caucasian male was referred to our Department from his general practitioner, because he suffered since several days from a continuous nasal purulent discharge. The history revealed an older brother who had died 2 years earlier of acute leukaemia, familiarity for type I diabetes, microcytemia, and glucose 6-phosphate dehydrogenase (G6PDH) deficiency. A slight mental handicap and an adenoidal aspect were evident. At anterior rhinoscopy the right nasal fossa was filled with a vegetating neoplasm, fleshy, friable and easily bleeding, which pushed the nasal septum controlaterally. At posterior rhinoscopy a thick, mucopurulent secretion was visible behind the neoplasm, at choanal level. Swollen nodes were palpable bilaterally in the neck, the rest of physical examination being negative.

A biopsy of the mass was taken together with a swab of nasal secretion *(Proteus mirabilis)*, an antibiotic treatment was set and a CT scan of the paranasal sinuses was performed to better evaluate the site and extension of the mass.

The CT showed that all right paranasal cavities were totally occupied by a formation with soft tissue density arising in the right nasal cavity, with lateral displacement and erosion of ethmoidal cells, medial maxillary and orbital walls. All right paranasal cavities and the rhinopharynx were involved, with displacement of the septum and the medial wall of maxillary sinus (Figures 1 and 2). Together with the history, the clinical aspect of the mass and its radiological appearance were strongly suggestive of a malignancy.

The histology of tissue fragments revealed, in fact, a proliferation of atypical cells with a big, hypercromic nucleus, often in mitosis. Such elements appeared aggregated to form solid nests, intermingled with evident necrosis (Figures 3a and b). Immunohistochemistry showed a marked positivity of these cells for CAM 5.2 low-molecular-weight cytokeratin, CD30, placental alkaline phosphatase [PLAP] and HPL, suggesting the diagnosis of EC (Figures 4a and b). Serologic tests detected a high level of the beta-subunit of human chorionic gonadotropin, [β-HCG] (53.000 mUI/ml, normally absent), while the level of other markers specific for EC resulted normal (α-feto protein [AFP]: 1.06 ng/ml, n.v.<20 and carbohydrate antigen 19-9 [CA19.9]: 14.12 U/ml, n.v.<37).

All further radiological (chest and mediastinal X-rays, testicular, abdominal and pelvic sonography, brain, thoracic, abdominal and pelvic CT) and clinic (internistic, urologic and ophthalmologic consultations) examinations ruled out any other metachronous locations, confirming the exclusive nasal onset of the neoplasm.

The patient was therefore submitted to a chemotherapeutic treatment. After 4 courses of PEB (Platinum 20 mg/m^2, Etoposide 100 mg/m^2 and Bleomycin 18 mg/m^2), administered in 5 days and repeated after 3 weeks, serum levels of β-HCG gradually decreased, being undetectable at the end of the last course. A CT scan confirmed the dramatic response to the treatment (Figure 5), with endoscopic traces of residual pathologic tissue.

Two other courses of chemotherapy were thus administered, following the same protocol, but using PEI (Platinum 40 mg/m^2 days 3-5, Etoposide 100 mg/m^2 days 3-5 and Ifosfamide 2 g/m^2 days 1, 2), the latter being preferred to Bleomycin to avoid possi-

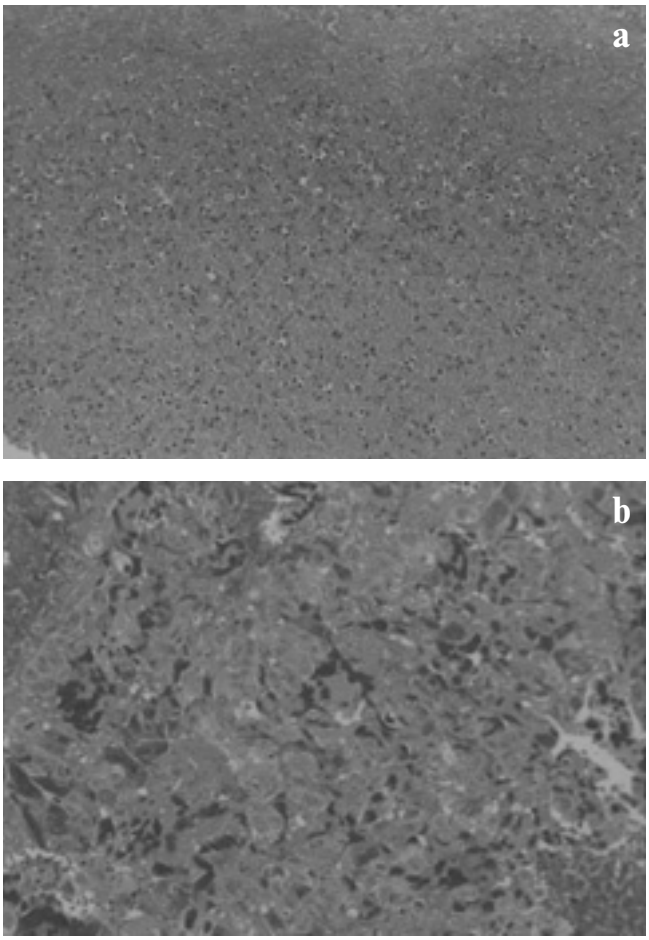

Figure 3. (a) The tissue appears infiltrated by elements aggregated to form solid nests, intermingled with evident necrosis. (HE, 200X). (b) : at a higher magnification, the proliferation of atypical cells with a big, hypercromic nucleus, often in mytosis, is evident. (HE, 400 X).

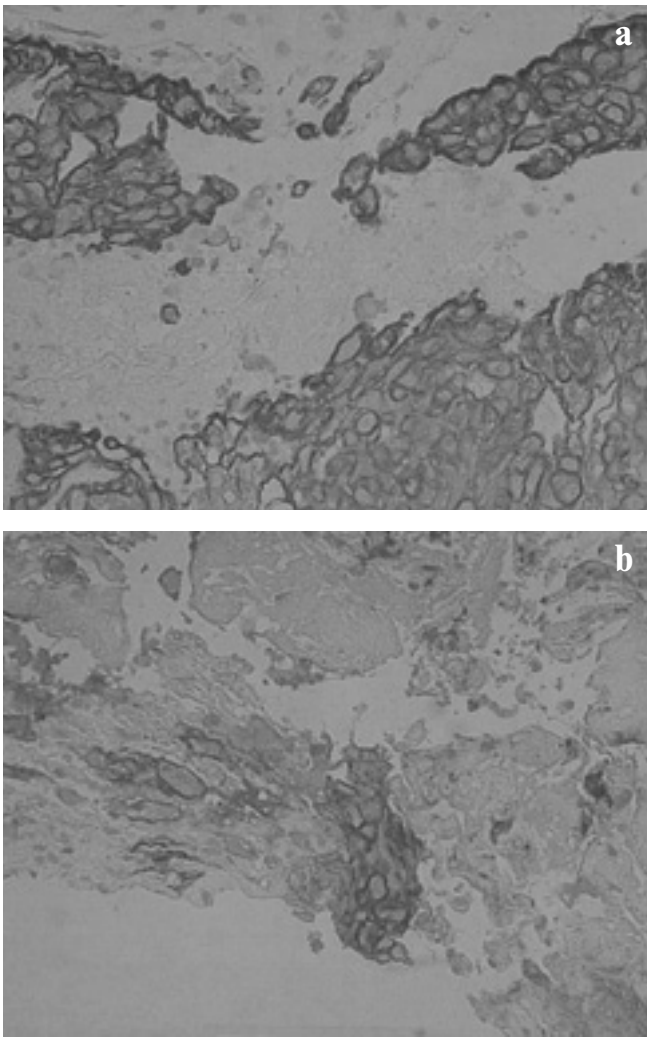

Figure 4. Typical features in immunohistochemical staining showing immunoreactivity for (a) cytokeratine and (b) placental alkaline phosphatase (PLAP) (IHC, 400X).

ble pulmonary side effects reported after high dosage [10]. Serial glomerular filtration rates were performed during the treatment. Audiometric and pulmonary function tests were normal too.

As at endoscopy pathological tissue was still evident, we decided to perform an endoscopic ethmoidectomy and antrostomy to remove the residual disease and limit the toxicity of further chemotherapy. Histological examination of the resected tissue did not reveal any sign of neoplasm, but only chronic inflammation. No intra- or postsurgical complications occurred, and the patient was discharged 4 days after surgery. After six months, a hypertrophic tissue was endoscopically detected in the infero-medial aspect of the maxillary sinus. A biopsy was performed through the antrostomy, revealing again the presence of chronic inflammation.

The boy has been followed-up endoscopically every month, and neither serologic markers nor periodic CT scans revealed signs of recurrency up to now.

DISCUSSION

Nasal fossae malignancies are generally represented by squamocellular carcinomas (70%), with various degrees of differentiation, the remaining 30% being constituted by adenocarcinomas, malignant lymphomas and others (esthesyoneuroblastomas, fibrosarcomas, condrosarcomas, melanomas and rabdomyosarcomas [12,31,32]. Both their site of onset and histology determine the prognosis, while surgery and/or radiotherapy act as first-line therapy for most of them.

In the case here reported, serological tests detected a high level of β-HCG, indicating a germ cell origin of the tumour [9,28,33-36], while the level of other markers normally present in such neoplasms (AFP and CA19.9) were normal.

Immunohistochemistry showed reaction to cytokeratine, CD30, placental alkaline phosphatase [PLAP] and HPL, confirming the serological indications and clearly addressing to an extragonadal germ cell origin of the tumour [33-35,37-39].

In previous reports about PEGCT, CD30 has consistently been found strongly expressed in EC [33,38] and absent in semino-

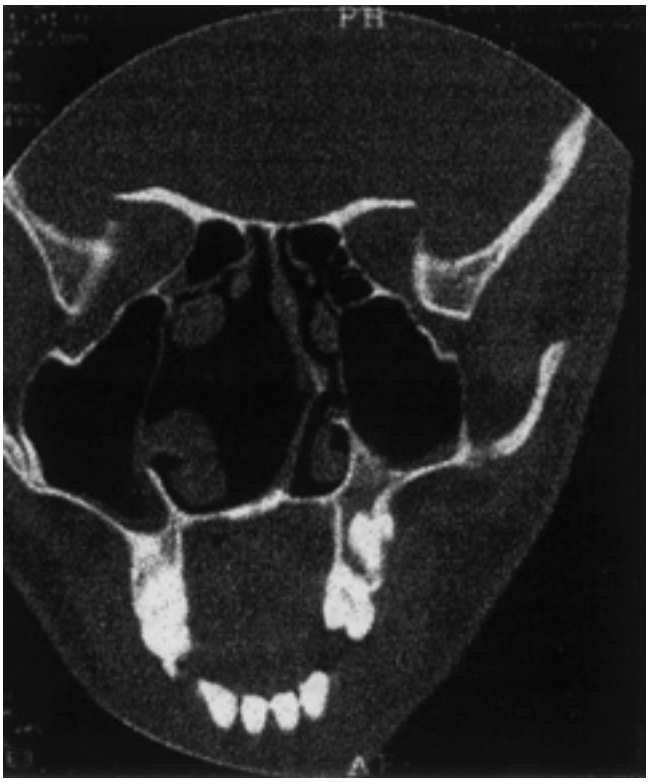

Figure 5. In the coronal cut the right nasal fossa and the maxillary sinus are free of disease.

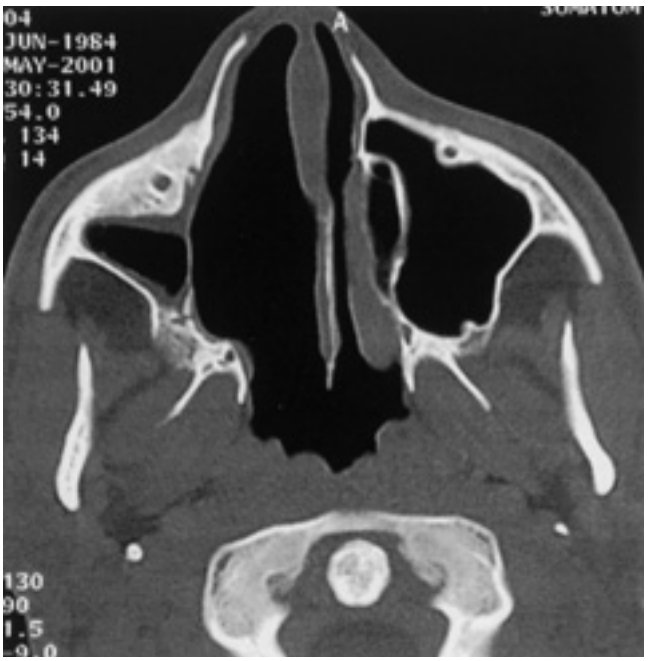

Figure 6. Axial CT scan after 3 years of onset: no signs of recurrencies are shown.

mas [37], while serum alpha fetoprotein (AFP) is generally elevated in all patients with yolk sac tumours [YST] [16]; on the other hand, there is evidence that CA 19-9 is constantly positive in EC, teratomas and seminomas, and negative in choriocarcinomas and yolk sac tumours [40]. According to the literature, the CD 30 antigen has been shown to be regularly expressed in

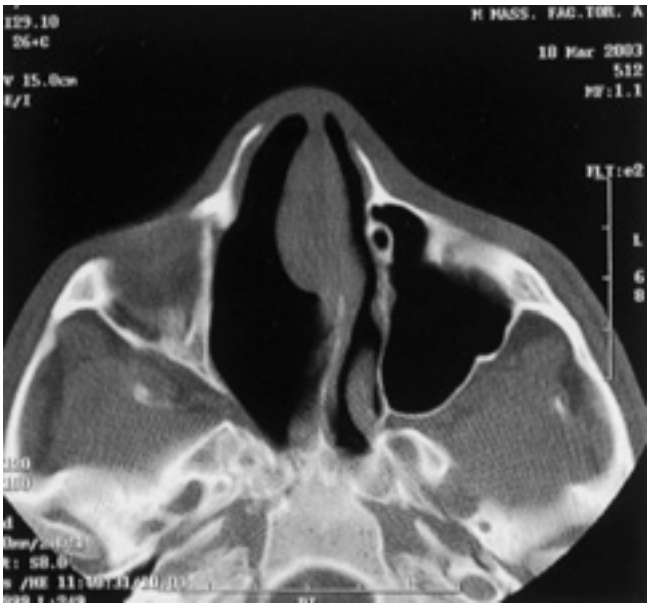

Figure 7. Axial CT scan 5 years after onset

EC [41], and capable of differentiating EC from other subtypes of extragonadal germ cell tumours [39]. On such basis, we could assume that we were facing the first primary embryocarcinoma arisen in the nasal fossa ever reported in the literature.

However, CD30 expression may not be necessarily restricted to embryonal carcinomas and occasionally may be observed in YST and seminoma cells, supporting the close histogenetic relationship that exists among these tumour types [33]. In fact, it has been recently hypothesized that CD30 expression in seminomas might indicate their upcoming transformation to EC [41].

From several sources cisplatin-based chemotherapy has been indicated as the first-line therapy for EC [24,26,42], followed by aggressive surgical resection of residual disease as one of the most successful models for the treatment of nonseminomatous germ cell tumours [11,25,27,43-45]. Other results indicated that adjuvant therapy consisting of combination of chemotherapy with cisplatin and etoposide and concomitant radiotherapy, followed by removal of the tumour, is highly effective in the treatment of pediatric patients with primary EC [23]. Others [46] reported a better prognosis in children with gonadal tumours treated with surgery alone. It has also been reported that about 20% of patients with germ cell tumour are still resistant to whatever therapy [47].

Five-year overall survival after cisplatin-based chemotherapy has been 89% for seminomatous EGCT, only 47% for non-seminomatous ones [29]; among the latter, retroperitoneal locations responded better than those with mediastinal onset (91% and 60%, respectively) [30]. Recently, an overall response rate of 83.3% has been reported [6]. Survival in patients with gonadal primaries (76%) exceeded that in patients with extragonadal primaries (47%). Survival in patients with localized disease (74%) exceeded that in patients with regional extension or metastases (47%)[48], indicating that tumour location is important in deter-

mining prognosis, whereas tumour histology is not.

Though elevation of HCG, as chemorefractory condition, has been associated with significantly poor survival [9,28,49], we preferred to start with intensive PEB/PEI chemotherapy, reserving the surgical option once residual or recurrent disease would have been evident. We could actually evaluate the quality of response of the malignancy to chemotherapy monitoring HCG levels decline between each course. In fact, this tumour marker has been examined for its utility as prognostic indicator: apart from its level at diagnosis, the finding of a delayed rate of decline suggests a poorer response of the malignancy to chemotherapy [50]. The gradual decrease of HCG level in our case (from 53.000 mU/ml to 0.61 mU/ml after 3 PEB courses, 0 mU/ml after 4 PEB courses), together with the parallel radiological result encouraged us to avoid surgery at that time, that would have required a radical approach with severe and permanent aesthetic and functional sequelae. Two more courses of chemotherapy, modified to limit toxicity, got rid of the neoplasm, as confirmed by serology, histology and CT.

In the last control, the patient did not refer symptoms of nasal obstruction, nor were signs of altered ostio-meatal drainage seen at CT (Figure 7). Should those be detected in the future, a septoplasty could be planned.

According to the literature [47,48], the success of the treatment seems to confirm, in this case, that the primary site of a tumour represents the only independent prognostic factor for survival.

CONCLUSIONS

PEGCT are rare neoplasms with generally poor prognosis, different behaviour, and natural course compared to their gonadal counterparts. Both primary and salvage treatment of these tumours constitute a challenge.

The evidence of an EC with nasal onset is exceptionally rare. Going through the international literature of the last 40 years, assessed from the most up-to-date data banks, we could not found a single paper or clinical report of such a location.

The lack of other reports on this subject could have at first biased our strategy, as EC has shown to be responsive, in other sites of onset, to a combination of chemotherapy, radical surgical excision of the neoplasm, and radiotherapy. Most extragonadal germinal tumours respond to a multimodal therapy, based on radical surgery after platinum-based chemotherapy.

Despite previous studies called for a multimodal therapy, the good response to chemotherapy, confirmed by imaging and laboratory tests, made surgery avoidable at that point.

If we take in account the reasonable follow-up period (5 years), during which clinical examinations, CT scans, and laboratory tests did not show any sign of recurrence, we can assess that the disease has been controlled, despite the malignant feature of the neoplasm.

In the case reported here, this unusual location of EC responded exclusively to primary chemotherapy; the histological pattern of residual pathological tissue surgically removed after six courses of chemotherapy revealed, in fact, the presence of chronic inflammation.

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