



Sadler, K. A., Hanna, C., Melia, L. and White, J. (2020) Very unusual case of a primary sinonasal germ cell tumour. *BMJ Case Reports*, 13(2), e232288.

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Deposited on: 5 March 2020

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## TITLE OF CASE

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A very unusual case of a primary sinonasal germ cell tumour

## SUMMARY

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Sinonasal malignancies are a very rare diagnosis. We present a unique case of a 32 year old man who presented with symptoms of worsening sinusitis and periorbital cellulitis. Investigation found a sinonasal malignancy and pathology confirmed this to be a primary germ cell tumour. The patient was managed with chemotherapy, surgery and consolidation radiotherapy and has remained well to date. This case report outlines an unusual presentation and diagnostic challenge for the primary care physician, ENT surgeon, pathologist and oncologist with review of the surrounding literature.

## BACKGROUND

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Sinonasal malignancies are a rare tumour group. When they do occur, they tend to present in older men and are most likely to be either squamous cell carcinoma or adenocarcinoma. Germ cell tumours tend to occur in younger people and are most commonly found in the testicles, ovaries or with occasional presentation at extragonadal midline sites, commonest being the retroperitoneum. We present a case of a 32 year old man with no significant past medical history who was diagnosed with a sinonasal malignancy. Further investigation found this to be a primary germ cell tumour. His clinical presentation, histology, tumour site and subsequent treatment establish this as a unique case in the literature.

## CASE PRESENTATION

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A 32 year old gentleman presented to his GP in July 2018 with problematic nasal congestion and pain. These symptoms failed to respond to treatment with antibiotics, antihistamine nasal sprays and eye drops. After seven weeks, the patient presented to the emergency department acutely with new symptoms of swelling in both eyes, feeling feverish with a headache. He had no significant past medical history, was on no regular medications, a non-smoker, drank little alcohol and had no significant family history. He was married with one daughter.

On examination he had a temperature of 39.5°C, right periorbital swelling with proptosis and was having difficulty opening his right eye. Bloods tests were normal except for; WCC 26.3 (4.0-10.0 x10<sup>9</sup>/l), Neutrophils 25.0 (2.0-7.0 x10<sup>9</sup>/l), Lymphocyte count 0.4 (1.1-5.0 x10<sup>9</sup>/l), CRP 162 (0-10 mg/L), total bilirubin 33 (<20 umol/L). The patient was treated with intravenous antibiotics and a computerised tomography (CT) scan was performed as per local protocol for severe periorbital cellulitis. CT results prompted an urgent MRI head.

Scans demonstrated a large (40x43x56mm) heterogeneously enhancing mass centred on the ethmoid air cells with intracranial extension and adjacent vasogenic oedema within the frontal lobes inferiorly. Additionally, there was extension into both orbits and indentation on the medial recti muscles bilaterally. Significant fluid and debris were seen in the paranasal sinuses, secondary to obstruction of osteomeatal complexes from the mass lesion. Craniocervical junction and CSF spaces were unremarkable (Figure 1a). Appearances radiologically were in keeping with an extensive sinonasal tumour.

Bedside biopsy was performed following administration of local anaesthetic and decongestant spray using a headlight and rigid nasoendoscope. Microscopy showed fragments of fibrous connective tissues extensively infiltrated with poorly differentiated tumour cells. There was heterogeneity within the biopsy specimen with some areas showing cells with well spaced, squared off nuclei with cytoplasmic clearing and some areas of necrosis, brisk mitotic activity and nuclear crowding indicating higher grade disease. Keratinisation, gland formation or any evidence of a sarcomatoid element were not identified. Immunohistochemistry staining for OCT3/4, PLAP, CAM 5.2 and AE1/3 were positive. Staining was negative for CD45, NSE, S-100, Melan-A, AFP, Glycican-3, CD30, CD34, CD117.

OCT3/4 (octamer-binding transcription factor 3/4) is expressed by embryonic stem cells and germ cells; PLAP (Placental alkaline phosphatase) is an enzyme which is normally present within the placenta in the third trimester of gestation; CAM5.2 is a cytokeratin stain that often shows positivity in epithelial tumours and AE1/3 is a pankeratin stain is also positive in epithelial tumours.

The OCT3/4 and PLAP positivity indicated that this was likely to be a germ cell tumour. Subclassification into seminoma or non-seminomatous disease was challenging however because although some areas within the tumour morphologically resembled seminoma, strong cytokeratin positivity and absence of CD117 is unusual in this disease entity. The areas of higher grade morphology on microscopy raised the possibility of embryonal carcinoma or yolk sac tumour, but the absence of CD30 staining ruled out the former and negativity for AFP/Glypican 3 the latter (Figure 2a & Figure 2b).

Slides were sent to Professor Reuter at the Memorial Sloan Kettering Cancer Centre in New York for specialist review who agreed this was a complicated case but favoured a poorly differentiated neoplasm with epithelial differentiation. No definite diagnosis could be reached.

Further laboratory tests showed a serum beta-human chorionic gonadotropin (B-HCG) of 741 (<5 U/L), lactate dehydrogenase (LDH) of 139 (80-240 U/L) and an alpha-feto protein (AFP) of <3 (<7 kU/L). Testicular ultrasound showed normal testes and epididymis with a small right sided hydrocele and CT scan of the patient's chest/abdomen/pelvis did not reveal any nodal or metastatic disease.

Review of the clinical presentation and demographics of the patient, laboratory results, radiological findings and pathological information concluded the most likely diagnosis was a germ cell tumour. The differential diagnosis at this point was a rare primary sinonasal presentation of a primary germ cell tumour, extension from a primary germ cell tumour originating in the central nervous system, or a metastatic deposit from a distant primary site in the midline such as gonadal or extragonadal with regression of the primary at diagnosis.

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PET-scan, sperm storage and baseline audiology tests were organised urgently as the standard work up prior to treatment with systemic chemotherapy. Unfortunately, whilst awaiting these investigations, the patient suffered a prolonged grand-mal seizure. High dose intravenous steroids and leviteracetam were commenced. He was also started on prophylactic co-amoxiclav given the sino-nasal invasion and subsequent risk of anaerobic infection. A repeat CT head scan (6 days after the initial scan) showed a marginal increase in the size of the intracranial component although the quantity of oedema was similar

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## **DIFFERENTIAL DIAGNOSIS *If relevant***

Initial differential diagnoses included sinusitis, periorbital cellulitis or underlying malignancy. Later on, the differentials were a rare primary sinonasal presentation of a primary germ cell tumour, extension from a primary germ cell tumour originating in the central nervous system, or a metastatic deposit from a distant primary site in the midline such as gonadal or extragonadal with regression of the primary at diagnosis.

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## **TREATMENT *If relevant***

### Initial treatment

The risk of neurological deterioration if treatment was delayed was weighed up against the benefits of having the optimal staging/work up investigations and it was felt that delaying chemotherapy could lead to significant morbidity. The optimal choice of chemotherapy regime was deliberated: BEP (bleomycin, etoposide, cisplatin), C-BOP-BEP (carboplatin, bleomycin, vincristine, cisplatin followed by bleomycin, etoposide and cisplatin) and VIP (etoposide, ifosfamide and cisplatin) were all considered.[1-3] On balance, given the intra-cerebral disease involvement, VIP was chosen because of its superior CNS penetration [etoposide 75mg/m<sup>2</sup> days 1-5 (D1-5), ifosfamide 1200mg/m<sup>2</sup> (D1-5) and cisplatin 20mg/m<sup>2</sup> (D1-5)].

By day 7 of cycle 1 of VIP chemotherapy treatment, the patient's visual symptoms had normalised and by the end of cycle 1 his nasal passages had cleared. B-HCG levels were normal by the end of cycle 2 and there was no further seizure activity (Figure 3).

The patient completed four cycles of VIP chemotherapy and end of treatment CT showed a good response to treatment with significant reduction in the size of the prior noted ethmoid air cell tumour (Figure 1b). However, some residual inflammatory changes within the ethmoid air cells were identified, there was multifocal bony dehiscence with chronic inflammatory change and the possibility of residual tumour infiltration remained. These images were reviewed at a multidisciplinary meeting to decide ongoing management.

### Subsequent treatment

Three months after initial presentation and 3 weeks after the last cycle of chemotherapy, surgical resection of the areas of possible residual tumour was performed to ascertain the exact nature of the tissue that did not respond. Focal residual viable germ cell tumour in the right anterior skull base tissue was detected in the surgical specimen; there was tumour extending up through the skull base which was not resected due to concerns of causing a dura breach, CSF leak or CNS contamination which would have delayed ongoing management.

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After discussion at a national multidisciplinary meeting it was felt that local radiotherapy alone after chemotherapy would not be sufficient consolidation treatment, and that radiotherapy to both the local site and the craniospinal axis was required. The patient consented to receive craniospinal radiotherapy (CSRT) after being informed of the likely acute side effects which included headache, nausea, diarrhoea, fatigue, alopecia, bone marrow suppression, a temporary reduction in sperm count and decreased hearing. Whilst receiving radiotherapy, the patient had significant issues with pancytopenia requiring blood product support. He received a total of five units of packed red cells and three units of platelets.

Due to the unusual location of the primary disease, acute side effects also envisaged included those more in keeping with radiotherapy delivery to the head and neck region. These include pain and crusting of the nasal passages, painful mouth, decreased taste and smell, itchy eyes (due to corneal dose), sore throat, hoarse voice, dysphagia and oesophagitis. Potential long-term side effects of CSRT were explained to the patient; decline in short term memory, pituitary dysfunction, stroke, chronic gastritis and gastric ulcers, development of benign tumours such as meningioma and secondary malignancy. Again, due to the location of the primary disease and radiotherapy boost, additional long term side effects explained were a loss of smell, a dry nasal passage, dry eyes and cataracts. The proximity of the primary disease to the pituitary and optic chiasm means that this patient is at risk of pituitary dysfunction and visual loss in the future.

Consolidation cranio-spinal radiotherapy (CSRT) was commenced 11 days after the surgical procedure. The risk of long term toxicities led to dose constraints. 35Gy in 20 fractions of photon radiotherapy was delivered to the craniospinal axis using a volumetric rapid arc intensity modulated technique followed by a boost of 20Gy in 12 fractions to the site of gross sinonasal disease at presentation (Figure 4). Using VMAT the dose to the optic chiasm was kept below 54Gy which confers a longer term risk of visual loss in the region of 1-2%.

## OUTCOME AND FOLLOW-UP

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This patient is now recovering from intensive treatment with normal tumour markers and will be followed up regularly by the medical oncologists, radiation oncologists and ENT team. Five months on from completion of treatment an MRI showed no sign of recurrence.

Given his treatment with long term high dose steroids and radiation exposure, a referral to the endocrinology team will be required at 6-9 months post-diagnosis to assess pituitary function and the need for ongoing hormone supplementation.

## DISCUSSION *Include a very brief review of similar published cases*

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Sinonasal malignancies are incredibly rare; making up 1% of all cancers. Only 400 cases are diagnosed in the UK each year with a worldwide annual incidence of 1 in 100,000.[4,5] More than seventy benign or malignant tumours and tumour-like conditions have been identified.[6] The maxillary sinuses and nasal cavity are the most commonly encountered sites of disease, but tumours are also found in the ethmoid, sphenoid and frontal sinuses. Patients with sinonasal tumours typically present with nasal obstruction followed by facial swelling and epistaxis.[7] They often have

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fairly advanced disease at time of presentation.[8,9] Risk factors include exposure to tobacco smoke, air pollution, hardwood dust, formalin, exposure to nickel toxins and leather/textile production.[10] There can be significant overlap between clinical and radiological features of benign and malignant disease in the nose, making diagnosis difficult.[11] Sinonasal malignancies are most commonly seen in males and peak in incidence at age 50-70.

Pre-treatment biopsy is an essential step in management.[12] The most common histological subtypes of sinonasal malignancy are squamous cell carcinoma and adenocarcinoma.[13] Other histologies include sarcoma, undifferentiated carcinoma, teratocarcinosarcoma, malignant melanoma, adenoid cystic carcinoma, lymphoma, olfactory neuroblastoma, neuroendocrine carcinoma and nuclear protein in testis carcinoma.[14-17]

Germ cell tumours are a histologically and biologically diverse group of neoplasms. They primarily occur in the gonads but can develop at extragonadal sites in the midline of the body.[18] GCTs are usually identified as either seminomatous or non-seminomatous and then classified into three prognostic groups (good, intermediate or poor) given their primary site, extent of spread and tumour markers (AFP, LDH, B-HCG).[19,20] Despite having relatively low tumour marker levels, our patient had a primary sinonasal tumour with intracranial extension and was therefore classified as poor prognosis. Even when metastatic, cure rates in GCT are high. Five year survival rates of metastatic NSGCTs are 92%, 80% and 48% for good, intermediate and poor prognosis disease respectively. Good and intermediate prognosis metastatic seminomas have five year survival rates of 86% and 72%.

There have been very limited presentations of primary sinonasal germ cell tumours occurring in adults in the literature and publications tend to be limited to case studies.[21,22] A retrospective review of 123 patients with sinonasal malignancies (not exclusively GCT) found that there was no significant difference between survival rates in those treated with primary radiotherapy, primary chemotherapy or primary chemoradiation.[10] In a study looking at outcomes in 11,160 sinonasal tumour patients however, therapy with combination chemotherapy, radiotherapy and surgery provided favourable outcomes and improved overall survival.[16,23] A further review of 229 patients supported multimodality treatment, though acknowledged that prognosis is often poor.[7] Factors affecting prognosis are multifactorial and include age, gender and ethnicity as well as tumour location, histological type, grade and stage.[17] Should the tumour recur, it is most likely to do so locally and at an early stage in follow up.[23,24]

Our case demonstrates a unique presentation of a primary sinonasal GCT. Early and effective interaction between specialties was vital in providing best possible care in this very rare cancer presentation. Communication with the patient was also key given the unusual diagnosis, urgent need for intervention, potency of treatment and risk of significant short and long term side effects. Prognosis for this specific case remains guarded but the disease is felt to be potentially curable. Our patient will be regularly followed up by the ENT team, medical and clinical oncologists.

## LEARNING POINTS/TAKE HOME MESSAGES 3-5 bullet points

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- If a seemingly common illness is not responding to treatment it is worth considering if there is something more significant underlying.
- Once a rare disease is identified it is essential to involve the appropriate specialists as soon as possible in order to ensure timely and correct management.
- Maintaining a good relationship and regular communication with patients is of utmost importance when a diagnosis is uncertain or unusual.

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## FIGURE/VIDEO CAPTIONS

**Figure 1a Coronal MRI image at diagnosis**

**Figure 1b Coronal MRI image post-chemotherapy and pre-radiotherapy**

**Figure 2a - H&E stained section showing a high grade tumour morphology with necrosis and cytoplasmic clearing.**

**Figure 2b - strong nuclear immunohistochemical positivity for OCT3/4.**

**Figure 3 beta-HCG graph**

**Figure 4 Sagittal view of radiotherapy dose distribution at the 90% dose level.**

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## PATIENT'S PERSPECTIVE

This individual was obviously very surprised by his presentation, diagnosis and treatment. It all happened very quickly and he was unwell for a considerable amount of time. Now that he is recovering, he is grateful for all of the care he received and the efforts of medical and nursing staff to ensure he received the best possible treatment.

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