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Isolated leptomeningeal carcinomatosis and possible fungal meningitis as late sequelae of oesophageal adenocarcinoma

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| TITLE OF CASE |
| Isolated leptomenigeal carcinomatosis and possible fungal meningitis as late sequelae of oesophageal adenocarcinoma |
| AUTHORS OF CASE |
| Mr Richard Dumbill*, Dr Sanja Thompson, Dr Heiko C Peschl, Dr GDH Turner, Dr Charles Woodrow |
| SUMMARY |
| <p>We describe a case of a 67-year-old man with known COPD, Type 2 Diabetes Mellitus, hypertension, osteoarthritis, previous history of excess alcohol intake, and oesophagectomy three years earlier for T3N0 adenocarcinoma, referred by his general practitioner with confusion, weight loss, and several recent falls. CT chest-abdomen-pelvis revealed a right middle-lobe pulmonary embolism, while CT head revealed communicating hydrocephalus. Lumbar puncture was performed, and empirical treatment for TB and fungal meningitis was commenced. Unfortunately he suffered a rapid neurological deterioration with markedly elevated CSF pressures, leading to an external ventricular drain. Cytological analysis of a CSF sample revealed a cellular infiltrate consistent with leptomenigeal carcinomatosis (adenocarcinoma), with the previous oesophageal malignancy the likely primary. He passed away 17 days after hospital admission. Prolonged culture of CSF later produced evidence of two distinct phaeomycotic moulds (<i>Cladosporium</i> and <i>Exophiala</i> sp.), suggesting that fungal meningitis may also have contributed to the clinical picture.</p> |
| BACKGROUND |
| Oesophageal carcinoma is the 13 th most common malignancy diagnosed in the UK, with around |

9000 cases diagnosed each year[1] . The five-year survival rate is 15%[2] . Surgical resection is appropriate for approximately 1 in 5 patients[3], and includes oesophago-gastric resection, segmental oesophageal resection, and total oesophagectomy depending on the site of the tumour. Indications for primary surgical resection are T1 or T2 disease. Patients with T3 disease, and selected patients with T4a disease, may be offered resection after neoadjuvant chemoradiotherapy.

Neurological sequelae of oesophageal carcinoma are rare, and may be due to cerebral or leptomeningeal metastases, and paraneoplastic phenomena. Previous case reports illustrate the primary presentation of oesophageal carcinoma as classic meningitis[4]; malignant meningitis causing sensorineural hearing loss[5]; limbic encephalitis[6]; and confusion[7]. Recurrence following treatment has also been described presenting with haemorrhagic brain metastasis[8]. Here, we report the first case report of isolated leptomeningeal recurrence presenting as confusion, with rapid general deterioration and death, three years after apparently curative oesophagectomy for oesophageal adenocarcinoma.

CASE PRESENTATION

A previously independent 67-year-old man presented to the hospital after a home visit by his GP, who was concerned about confusion, weight loss, and several falls. The GP reported that his house was in a state of disrepair. His last contact with a healthcare professional had been four months previously with no cause for concern. His past medical history was significant for well controlled type 2 diabetes mellitus (as implied by HbA1c measurements from his GP up to four months prior to this presentation), hypertension, COPD, osteoarthritis, and oesophagectomy three years prior for adenocarcinoma of the gastro-oesophageal junction. Preoperative staging was T2N0M0, and he was treated with neoadjuvant Cisplatin and Capecitabine prior to a left thoracoabdominal oesophagectomy. Final pathological staging was T3N0M0.

On admission he was alert but confused, with an AMTS score of 3/10. His cardiovascular, respiratory, and neurological examinations were normal. He was thin and unkempt. He had no close friends or family who were able to provide a collateral history. He admitted to alcohol intake between 10-20 units per week. His medications included lansoprazole 30mg OD, sitagliptin 100md OD, amlodipine 10mg OD, insulatard 8-10 units OM, co-codamol, vitamin B12 supplements and inhaled salbutamol. His GP record indicated that his weight had been measured to be 77kg eight months prior to presentation, while in hospital his estimated weight was around 65kg. The initial impression was of acute delirium from urinary tract infection, likely superimposed on a chronic cognitive decline.

INVESTIGATIONS

Aside from confusion and cachexia, examination was unremarkable. The abnormal blood tests on admission were mild neutrophilia ($5.58 \times 10^{12}/L$), an INR of 1.8 (PT 20 seconds), an iron level of $4.2 \mu\text{mol}/L$, transferrin saturation of 8%, B12 level 1392 ng/L, low serum folate level ($<3 \mu\text{g}/L$), ALP 190 IU/L, CRP 11 mg/L, and a blood glucose of 17.8 mmol/L. Initial blood cultures were negative. He was treated with 10mg oral vitamin K, folic acid replacement and standard hospital alcohol detox regime (high vitamin B replacement) and chlordiazepoxide prn.

CT head revealed enlargement of the supra and infratentorial ventricular system, with significant parenchymal volume loss with no transependymal CSF resorption, and no acute injury (Fig. 1a).

CT chest, abdomen, and pelvis revealed a right middle lobe pulmonary embolism, and he was therefore anticoagulated. He received empirical treatment for a urinary tract infection with a course of oral co-amoxiclav. Over the following few days his cognition and mobility steadily

declined and intravenous acyclovir, amoxicillin and ceftriaxone were administered. An MRI scan (Fig. 1b, 1c) showed communicating hydrocephalus and brainstem atrophy, disproportionate to the patient's age, raising the possibility of an underlying neurodegenerative disorder.

A lumbar puncture performed on day 8 of his admission revealed an opening pressure of 7cm H₂O, and CSF biochemistry showed glucose of 3.7 mmol/l, (paired serum sample 12.3 mmol/l), lactate 11mmol/l, and a protein concentration of 1197 mg/dL. Microscopy revealed CSF WBC 34x10⁶/L (lymphocytes 30x10⁶/L). A BioFire® meningitis/encephalitis panel run on the CSF was negative and antibiotics and acyclovir were discontinued. The CSF sample sent for cytology was delayed in reaching the laboratory due to problems with labelling, which may have contributed to its degradation, showing only debris and poorly preserved cells, some of which were identified as small lymphocytes.

Clinical examination after lumbar puncture showed transient but significant improvement; he had progressed to being able to sit up and communicate in short sentences. He was reviewed by a neurologist, who suggested performing further laboratory analyses including VDRL, ANA, immunoglobulins, serum electrophoresis, beta-2-microglobulin, and paraneoplastic antibodies. We were also advised to arrange EEG, CT PET and after an interval repeat MRI brain and spine with gadolinium.

An autoimmune panel (run on serum and CSF) was negative for voltage-gated potassium channel antibodies, fixed cell NDMA receptor antibodies, and Hu, Yo, and Ri antibodies. Serum antibodies to HIV, syphilis, toxoplasma and *Borrelia* were negative and galactomannan was negative. The serum beta-d-glucan antigen level was above the normal range at 230 pg/mL.

This clinical improvement persisted for approximately five days, and was followed by general deterioration, with progressively impaired mobility. A lumbar puncture was repeated on day 15, revealing hypercellular CSF containing large, atypical cells with cytoplasmic blebbing, vacuolation, and basophilia, and once again high protein and low glucose. The beta-d-glucan concentration in the second CSF sample was elevated at 346 pg/ml. Empirical treatment for possible fungal and TB meningitis was commenced consisting of amphotericin, rifampicin, isoniazid, pyrazinamide, pyridoxine, and ethambutol.

On day 16 his GCS suddenly deteriorated to 4, and he was intubated and transferred to ITU. Repeat CT head showed global mass effect on paramedial sagittal plane with the loss of grey-white matter differentiation and sulcal effacement (Fig. 1d). On day 17, due to further deterioration and the development of sluggish pupils bilaterally, a third lumbar puncture was performed which showed an opening pressure of 37cm H₂O. Following this an external ventricular drain with intracranial pressure monitor was inserted, and a third CT head (Fig. 1e) following this showed progressive loss of grey-white differentiation consistent with extensive ischaemic/ hypoxic brain injury.

At this point cytology results from the second CSF sample became available. The CSF cytospin showed small mature lymphocytes and a variably sized population of atypical plasmacytoid cells with some nuclear enlargement, multiple nuclei and focal marked cytoplasmic vacuolation. Some perinuclear hoffs and deep cyanophilic cytoplasm were present. Flow analysis initially raised the possibility of a plasma cell malignancy; however, on immunostaining the enlarged atypical cells showed variable positive staining for pan-cytokeratin and CK7, in keeping with an epithelial adenocarcinoma. They were negative for lymphocytic markers CD3, C20 and CD79a, and plasma cell markers including MUM-1, cyclin D1 and CD56. No light chain staining or restriction was demonstrated, in keeping with the flow result. The features were felt to be those of a metastatic adenocarcinoma, which despite their plasmacytoid morphology and CD138+ on flow cytometry were felt likely to represent metastatic spread from the oesophageal primary. He continued to decline, and passed away later that day.

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| <p>Prolonged culture of the two CSF samples later yielded evidence of two distinct phaeomycotic moulds. <i>Cladosporium</i> sp. (confirmed by molecular identification) was cultured at the reference laboratory from the first sample. <i>Exophiala</i> sp. was identified by molecular methods from the second sample although failed to grow on subculture.</p> |
| <p>DIFFERENTIAL DIAGNOSIS</p> <p>The differential diagnosis changed as the case evolved, and included urinary tract infection, normal pressure hydrocephalus, an underlying neurodegenerative disorder, and intracranial infection. Early in the course of the admission the initial diagnosis of urinary tract infection was superseded by normal pressure hydrocephalus or a neurodegenerative process; however, his rapid deterioration was out of keeping with this. The lymphocytic nature of the CSF in combination with the appearance of hydrocephalus on brain imaging raised the possibility of a malignant meningitis, a lymphomatous meningitis, or a chronic infection such as TB or fungal meningitis. The diagnosis was complicated by the isolated nature of the pathology and a transient improvement after initial lumbar puncture and treatment for a possible UTI. The lack of lymphadenopathy on imaging initially suggested a pathology other than malignant or TB meningitis. CSF cytology eventually yielded the diagnosis, but only after repeated LPs, later in the course of his admission.</p> |
| <p>TREATMENT</p> <p>His treatment initially involved antibiotics for urinary tract infection, but his failure to improve, with further deterioration of cognition and mobility initiated further tests including brain imaging and lumbar puncture. The initial lumbar puncture revealed a normal CSF pressure, which contributed to a provisional diagnosis at this point of normal pressure hydrocephalus; therefore, earlier external ventricular drainage was not pursued. Treatment thereafter was guided by the test results – specifically, anti-tuberculous therapy was started due to clinical deterioration, the imaging findings, and a significantly lymphocytic CSF. Liposomal amphotericin was started due to the high beta-d-glucan levels in serum and CSF. Neurosurgical intervention with an extra-ventricular drain was eventually performed prior to definitive CSF cytology results becoming available, in response to rising CSF pressures and neurological deterioration.</p> |
| <p>OUTCOME AND FOLLOW-UP</p> <p>The patient unfortunately passed away on day 17 of his admission, after 2 days in intensive care.</p> |
| <p>DISCUSSION</p> <p>Our patient had evidence of both carcinomatous and fungal meningitis, both of which can cause chronic cognitive decline with more rapid deterioration associated with ischaemia and communicating hydrocephalus. Carcinomatous meningitis is a rare cause of delirium, and recurrence of a solid malignancy as isolated leptomeningeal metastases not visible on imaging is rarer still. Neurological complications resulting from leptomeningeal carcinomatosis secondary to a primary oesophageal cancer have previously been described[4,5,7] , but this is the first report of a recurrence presenting in this fashion. A possible mechanism for the development of leptomeningeal metastases without nodal disease could be dural injury and seeding at the time of resection; however the description of previous similar cases, particularly that described by Lobo et al. which presented with leptomeningeal seeding without any surgical intervention[7] raises the possibility that this could be a natural, rather than iatrogenic, phenomenon. Of note, in the case described by Lobo et al. lesser curvature, coeliac, and para-aortic lymphadenopathy was noted on CT scanning; in our case, no lymphadenopathy was found.</p> <p>No fungal agent was definitively identified <i>ante mortem</i>, but there were high serum and CSF</p> |

beta-d-glucan levels. In a study of CSF samples relating to a US outbreak of fungal meningitis associated with injection of contaminated methylprednisolone acetate, a CSF beta-d-glucan cutoff value of 138 pg/mL provided 100% sensitivity and 98% specificity[9]; our patient had a level well above this threshold. Prolonged CSF culture and molecular analysis later provided evidence of potential phaeomycotic mould infection involving *Cladosporium* and/or *Exophiala* species; both have been associated with cerebral abscess and meningitis in patients with immunosuppression, and our patient had several factors causing immunosuppression: malignancy, diabetes and severe weight loss. However, both of these are environmental organisms and hence there is a possibility that these findings represented culture contamination. It is already known that certain medical conditions and drugs can produce a false positive serum beta-d-glucan; could the same apply to CSF examination? Evidence on this is currently lacking but likely to grow substantially as this test is increasingly applied. Overall it is not possible to exclude the possibility that fungal meningitis contributed to the patient's clinical state, in addition to malignancy.

LEARNING POINTS/TAKE HOME MESSAGES

Oncological

- Neoplastic meningitis is suggested by clinical presentation consistent with meningitis or encephalitis, in conjunction with CSF showing a high lymphocyte count, high protein, and low glucose and negative microbiological investigations[7].
- A history of malignancy, particularly of large cell lymphoma, gastrointestinal, breast, lung, or melanoma increases the likelihood.
- Iatrogenic seeding could be considered as a possible mechanism when patterns of spread – particularly CSF infiltration with a lack of local or nodal recurrence – are atypical.
- MRI with contrast should be organized for cases suspicious malignancy. CSF examination is a valuable diagnostic tool in patients with suspected CNS malignancies, but due to its low sensitivity (initial sample positive in 45-94% of cases in previously reported series), negative results should not be ignored, and repeat sampling should be considered[10]. Likewise, its rapid transport to the lab and examination as soon as possible must be secured, in order to increase chance of successful diagnosis, as CSF specimens tend to degenerate rapidly[11].

Microbiological

- With the ever-increasing availability of sensitive microbiological diagnostics, it is inevitable that infectious agents will be implicated in an increasing proportion of chronic meningitis cases, so that in cases such as this one there may be laboratory evidence of more than one aetiology.
- It seems clear that measurement of the beta-d-glucan marker in CSF samples should be part of the standard workup in cases of chronic meningitis, and empirical antifungal treatment be given to cases with high levels while prolonged cultures are undertaken.
- Future research could help to determine whether beta-d-glucan can be falsely elevated in the presence of other conditions such as malignant meningitis.

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Figure captions

Fig. 1a CT head shortly after admission, reported as showing no acute intracranial pathology, with enlargement of the supra and infra-tentorial ventricular system, and no transependymal CSF resorption.

Fig. 1b MRI scanning showed ventriculomegaly (T2 weighted axial image).

Fig. 1c MRI showing brainstem atrophy (T1 weighted sagittal section).

Fig. 1d The CT scan (high resolution) immediately prior to EVD insertion, with global ischaemic changes and global mass effect on paramedial sagittal plane with the loss of grey-white matter differentiation and sulcal effacement.

Fig. 1e The CT scan (high resolution) post-drain. Despite aggressive ventricular decompression by the

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| drain, the changes shown in Fig. 1d had progressed on the subsequent post-drain CT. |
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