CASE REPORT

A benign cancer with malicious paraneoplastic syndromes

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SUMMARY

A 70-year-old retired general practitioner with known follicular lymphoma presented with ptosis, dysphagia and progressive weakness in his upper and lower limbs. Despite having positive antibodies for myasthenia gravis he did not respond to conventional treatment with pyridostigmine, immunoglobulins and steroids. After 1 week on a general ward, he required intensive care for non-invasive ventilation. On the intensive care unit, he developed a secondary paraneoplastic syndrome in the form of a syndrome of inappropriate antidiuretic hormone secretion and required a tracheostomy for ventilatory support. After 1 week of invasive ventilation and remaining fully conscious throughout, he declined further treatment and passed away.

BACKGROUND

Paraneoplastic syndromes occur with many forms of malignancy. We presented a case in which the paraneoplastic syndrome not only compounded the progression of the primary disease, but represented the leading cause of death. The association between non-Hodgkin's lymphoma and myasthenia gravis (MG) is rare and only a handful of cases have been described in the literature. Furthermore, our patient developed a pulmonary embolism as well as hyponatraemia likely caused by a syndrome of inappropriate antidiuretic hormone secretion (SIADH). He demonstrated rapid clinical deterioration and poor response to treatment. Having clinical insight into his disease being a medical practitioner himself, he made the voluntary decision to decline further treatment and subsequently passed away.

CASE PRESENTATION

A previously healthy retired general practitioner (GP) was diagnosed with follicular non-Hodgkin's lymphoma in 2005, after he had developed a painless swelling under his lower jaw. He was treated with local radiotherapy following excision of the tumour in his neck. After radiotherapy, mildly enlarged lymph nodes in the chest and abdomen regressed on follow-up imaging; these nodes were thought to have been reactive to the primary lymphoma. A bone marrow aspiration showed no infiltration; therefore the localised lymphoma was staged as Ia. He remained symptom-free in the following 3 years.

In 2008 an incidental prostate carcinoma was found. During the staging process, a CT scan revealed an enlarged abdominal lymph node. It was unclear at this point whether this lymphadenopathy was secondary to the prostate carcinoma or

part of the original lymphoma. A laparoscopic biopsy confirmed its origin as the follicular lymphoma rather than the new prostate carcinoma (subsequently graded as Gleason 4+4). The latter was treated with radical radiotherapy and an adjuvant 2-year course of zoladex. A later bone marrow biopsy did not show any infiltration and the staging was corrected to 3a. After a multidisciplinary meeting as well as discussion with the patient it was decided to follow a watchful waiting approach, as the patient remained symptom free at this point.

In 2012, the patient presented to his GP with a 6-week history of depression and right-sided ptosis as well as increasing weakness in his arms and legs. CT was performed and showed progression of his lymphoma. There was now lymphatic infiltration of the left renal hilum, small bowel mesentery and oesophagus. On admission he was reviewed by the neurology team, who found a right-sided partial ptosis with bilaterally restricted upgaze, left medial rectus weakness with diplopia on right gaze and fatigable left face weakness. In addition, a 3/5 proximal arm and 4/5 proximal leg weakness with hyper-reflexia was demonstrated. A repeat chest CT was performed to investigate increasing shortness of breath, which showed no abnormality of the thymus but revealed a concurrent pulmonary embolism. The patient was started on pyridostigmine and intravenous immunoglobulin, as well as an intravenous heparin infusion for his pulmonary embolism. He was breathless on minimal exertion and his functional vital capacity (FVC) was 2.3 L. Over the next 3 days an ultrasound-guided abdominal lymph node biopsy and a further bone marrow aspiration revealed invasion with the original follicular lymphoma. Coupled with significant weight loss, this changed the staging of his lymphoma to 4b. He deteriorated rapidly over the next 4 days despite on-going treatment. When his FVC reached 1.2 L he developed type II respiratory failure and was transferred to the intensive therapy unit (ITU) for ventilatory support, initially in the form of non-invasive bilevel positive airway pressure, but required a tracheostomy by the following day. Prior to insertion of the tracheostomy, a SIADH was suspected as evidenced by reduced plasma and increased urine osmolality and the low-plasma sodium concentration. The low-urine sodium presents an argument against the diagnosis of SIADH but this is not an exclusion criterion. There is no information available concerning

To cite: Vogt A, Wang S, Ventour D. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-008883

the cortisol metabolism of the patient at this point. Thyroid stimulating hormone (TSH) was within the reference range (see investigations). Unfortunately a T4 measurement was not performed at the time, but ideally should be, together with a cortisol profile, as part of the workup for SIADH. He was fluid restricted and his electrolytes improved. Approaching the 10th day of admission, our patient declined further escalation of treatment, in particular, inotropic support, but agreed to receive rituximab as a last attempt to salvage his lymphoma. Neither the rituximab and increased dose of pyridostigmine nor a 3-day course of high-dose steroids improved his condition. A ventilator-associated pneumonia was successfully treated with penicillin G. However, his myasthenia symptoms continued to deteriorate. Three weeks after admission, the patient, while still fully conscious and aware of his progressing disease declined any further treatment. Trials with other immunosuppressants as well as plasmapheresis were offered, but the patient requested us to refrain from further treatment. A one-way reduction of ventilator support was agreed between the medical team, the patient and his family. Our patient died on day 23 of his admission, receiving diamorphine to alleviate his shortness of breath in his last 12 hours.

INVESTIGATIONS

A CT scan performed on admission showed rapid progression of the disease in the abdomen and hilar region, and furthermore a pulmonary embolism was found. No evidence of thymoma was seen on this scan. The patient's forced vital capacity reduced from 2.3 L on admission to 1.6 L when transferred to ITU and 1.2 L when non-invasive ventilation was started.

On admission to ITU:

- ▶ Plasma sodium: 126 mmol/L (135–144)
- ▶ Plasma potassium: 4.3 (3.5–5.3)
- ▶ Plasma chloride: 89 mmol/L (96–109)
- ▶ Urine sodium: <10 mmol/L
- ▶ Urine potassium: 6 mmol/L
- ▶ Urine chloride: <15 mmol/L
- ▶ Urine osmolality: 126 mOsm/kg
- ▶ Plasma osmolality: 163 mOsm/kg
- ▶ Creatine kinase : 14 U/L (ref: 24–195 U/L)
- ▶ TSH: 2.8 (ref: 0.4–4.5 µU/L)

Antibodies:

- ▶ Voltage-gated calcium channels AB: negative
- ▶ Cerebellum AB: negative
- ▶ Thyroid peroxidase: 14 (ref: <75)
- ▶ MuSK-AB: negative
- ▶ Acetylcholine-receptor AB: 28 U/L (ref: undetectable)
- ▶ Cerebellum autoantibodies (Yo, Hu, Ri): negative

Biopsy result:

- ▶ CD10 Mib-1 (30%) CD19 bcl-1⁺ bcl-2⁺ p53^{neg} CD20 CD79 bcl-6⁺ CD23⁺ MUM-1⁺ FOX-P1⁺
- ▶ Follicular lymphoma common type (9690/3)

DIFFERENTIAL DIAGNOSIS

The presentation of his symptoms points clearly to an underlying myasthenic syndrome and myasthenia gravis. Unfortunately the antibody results only became available after his death. They confirmed a MuSK⁺ and acetylcholine-receptor⁺ myasthenia gravis.

TREATMENT

The patient received an acetylcholinesterase inhibitor as well as immunoglobulin until 2 days before his death. He was also treated with a short course of high-dose steroids and rituximab as a final salvage treatment in the hope that improvement of his lymphoma would concurrently mitigate his myasthenia symptoms.

OUTCOME AND FOLLOW-UP

The patient denied further treatment 3 weeks after admission and died of respiratory failure.

DISCUSSION

With a prevalence of only 200–700 cases/million¹ MG is a comparatively rare condition, but only a handful of cases have been described for MG appearing in the context of lymphoma.² Of the 21 known cases summarised in a recent review² 19 improved under treatment and 2 deaths were cases unrelated to the myasthenia. Eighteen of them were positive for acetylcholine receptor antibodies and one for the MuSK antibody. In four of these cases the lymphoma was follicular. In all cases there was a close temporal association between the occurrence of the two diseases. This suggests that MG can occur as a paraneoplastic syndrome.² Improvement of the myasthenic symptoms is described in most cases where the lymphoma is controlled.² Unfortunately this did not apply to our case, since the patient passed away before disease or symptom control could be achieved. Besides the temporal proximity and the improvement under treatment, MG associated with lymphoma appears to present with a generalised symptomatic picture including bulbar symptoms, respiratory depression and proximal limb weakness. This is reflected in our particular case. A paraneoplastic MG with only ocular symptoms has not been described.

An increase in autoimmune disease has been observed with non-Hodgkin's lymphomas (NHL). MG is not the only autoimmune condition associated with NHL. Rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome and autoimmune thyroid diseases have been known to be linked to NHL.³

It should be noted that the paraneoplastic MG is distinctly different from the condition known as Lambert-Eaton myasthenic-syndrome (LEMS), since the putative underlying pathogenesis is not molecular mimicry as in the case of LEMS but a modulation of humoral immunity.

The close temporal association of MG with a relapse of the lymphoma makes an association in our case likely. It is true, however, that the patient was at an age that is typical for manifestation of MG.¹ Conversely, we were unable to find any evidence of other underlying causes of MG (eg, a thymoma). What makes our case significant is the rapid progression of the myasthenic symptoms leading to the death of the patient in only 3 weeks after admission despite intensive medical treatment. Interestingly it was not the underlying malignant lymphoma that caused the biggest challenge for this gentleman, but the complications occurring in short sequence: first MG, followed by a pulmonary embolism and a likely SIADH. In the end, it was the refractory respiratory symptoms and ventilator dependency that prompted our patient to decline any further treatment. We accepted his decision after multidisciplinary discussions. Possible unexplored therapy options such as plasmapheresis and immunosuppressants exist; however, the efficacy of these would be doubtful given our patient's critical clinical condition.

Learning points

- ▶ Myasthenia gravis (MG) can occur as a paraneoplastic syndrome of lymphomas.
- ▶ Treatment of MG includes acetylcholinesterase inhibitors, steroids, immunoglobulins, immunosuppressants and plasmapheresis.
- ▶ A paraneoplastic syndrome can affect management irrespective of staging of the primary cancer.
- ▶ Paraneoplastic MG appears to present as a generalised form rather than limited to ocular symptoms.

Acknowledgements The authors would like to thank Maaz Babiker, Zenna Trant, Mohsin Siddiqui, Katrina Crawford, junior doctors working on the critical care unit, and Tom Cowlam consultant in intensive care.

Contributors AV wrote the article and performed the literature research, DV and SW critically revised the article and gave expert advice.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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