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Case Report

The diagnostic maze of synchronous mass lesions in brain and lung

Theingi Aung^a, David Ford^b, Michael Hardmann^d, Mohan Hingorani^{c,*}

^a Specialist Registrar (Clinical Oncology), Castle Hill Hospital, UK

^b Consultant (Respiratory Physician), Scarborough General Hospital, UK

^c Consultant (Clinical Oncologist), Castle Hill Hospital, UK

^d General Practitioner, Practice 2 Medical Centre, Bridlington, UK

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published case reports of SR of lung cancer with brain metastasis. Furthermore, there are other pathological possibilities with higher probability of SR on steroids compared to lung cancer. This case report highlights the diagnostic maze surrounding the presence of synchronous mass lesions in the lung and brain and underscores the importance of pursuing histopathological confirmation in these circumstances.

Case report

Introduction

We report on an interesting case of spontaneous-regression of synchronous mass lesions in the lung and brain. The patient was discussed in a multi-disciplinary environment and the diagnosis of lung primary with brain metastasis was made based on the radiological and clinical presentation and the patient was commenced on steroids for symptomatic relief in the absence of histopathological confirmation. However, the lesions spontaneously regressed more than 15 months after initial presentation. Spontaneous regression (SR) of malignancy is an intriguing phenomenon that has been described particularly in the context of renal, melanomas and haematological malignancies. However, SR of lung cancer is an unusual phenomenon and there are no

In January 2013, an 81-year-old female patient presented with few weeks history of vomiting, unsteadiness and difficulty in writing. There was no recent history of any head trauma, seizures or loss of consciousness. She denied any systemic symptoms of fever, cough and shortness of breath, alteration of bowel habit, weight loss, or rash. Past medical history included hypertension, iron deficiency anaemia, hiatus hernia, and osteoarthritis. In July 2010, she was diagnosed with sero-negative rheumatoid arthritis and was commenced on methotrexate. The patient was investigated three months earlier for self-limiting back pain with weight-loss and underwent comprehensive screening for probable infection with negative cytomegalovirus IgM, Hepatitis B surface antigen and Paul-Bunnell test excluding acute Epstein-Barr virus (EBV) associated infection. During her admission she was taking methotrexate 25 mg/week and her other medications included amlodipine, bendroflumethiazide, lansoprazole, enalapril, gaviscon, codeine, paracetamol, cyclizine and furosemide. She never smoked.

* Corresponding author. Tel.: +44 1482 461303.

E-mail address: mohan.hingorani@hey.nhs.uk (M. Hingorani).

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Table 1 – Temporally ordered display of laboratory investigations.

September 2012	CMV IgM antibody	Not detected
	Toxoplasma IgG	Not detected
	Hepatitis B surface antigen	Not detected
	Hepatitis C antibody	Not detected
	Paul Bunnell	Negative
February 2013	Haemoglobin	9.7 g/dl
	White cell count	$17.0 \times 10^9 \text{ L}^{-1}$
	Neutrophils	$14.89 \times 10^9 \text{ L}^{-1}$
	Platelets	$585 \times 10^9 \text{ L}^{-1}$
	MCV	88.3 fl
	Sodium	134 mmol/L
	Potassium	4.4 mmol/L
	Urea	9.7 mmol/L
	Creatinine	106 $\mu\text{mol/L}$
	Corrected calcium	2.41 mmol/L
	Serum iron	5.0 $\mu\text{mol/L}$
	Serum ferritin	184 $\mu\text{g/L}$
	Serum B12	453 ng/L
	Serum folate	13.8 $\mu\text{g/L}$
	Total bilirubin	7 $\mu\text{mol/L}$
	Alanine-transaminase (ALT)	16 IU/L
	Alkaline-phosphatase (ALP)	69 IU/L
	Albumin	34 g/L
	CRP	5.4 mg/L
	TSH	0.58 mU/L
	Plasma viscosity	1.74 (normal)
January 2015	EBV EBMA IgG	Positive
	AMCA	Negative
	Anti-nuclear Ab	Negative
	Cardiolipin IgG	<2.0 GPL (0.0–19)
	Anti- $\beta 2$ Glycoprotein (IgG)	<1 μmL (0–19)
	IgA	1.45 g/L (0.80–4.00)
	IgG	6.4 g/L (6.0–16.0)
	IgM	0.50 g/L (0.50–2.00)
	Paraprotein	Not detected

She drank 7 units of alcohol per week and there was no family history of malignancy.

She was conscious and orientated in time, place and person and physical examination showed normal cardio-respiratory

system. Neurological examination revealed positive cerebellar signs with wide-based gait, past pointing and positive heel shin test.

Investigations

The patient underwent comprehensive array of laboratory investigations as summarised in Table 1. The chest radiograph was reported as normal, but the contrast-enhanced computed tomography (CT) of chest, abdomen and pelvis demonstrated multiple scattered lesions in bilateral lung fields, the largest lesion measuring $2.8 \times 1.3 \text{ cm}$ in apical segment of right lower lobe with spiculated margins strongly suggestive of primary lung malignancy. There was no significantly enlarged mediastinal or hilar lymphadenopathy. Below the diaphragm there was evidence of $2.5 \times 2.2 \text{ cm}$ hypo-attenuating lesion in the posterior spleen.

Subsequently, she had magnetic resonance imaging (MRI) of the head with gadolinium that showed heterogeneous peripherally enhancing lesions on T1-weighted sequence in right cerebellar hemisphere and left occipital and parietal lobes with corresponding increase in T2WI signal reflecting marked surrounding peri-lesional oedema and localised mass effect on the occipital horn and body of left lateral ventricle (Figs. 1 and 2).

Treatment, outcome and follow-up

The case was discussed in Lung and Neurosurgical Multi-disciplinary Team (MDT) meetings and there was overwhelming consensus on probable diagnosis of lung malignancy with brain metastasis. In view of patient's frailty and co-morbidities and reservations about her ability to tolerate active oncological therapy it was decided not to pursue histopathological confirmation as it was unlikely to change overall management and prognosis. The patient was commenced on dexamethasone 4 mg once daily to reduce the cerebral oedema and

Fig. 1 – Contrast-enhanced (gadolinium) MRI showing SR of cerebral lesions. MRI in February 2013 demonstrated T1-weighted contrast-enhancing lesion (yellow arrow) in left occipital region (A) and right cerebellar hemisphere (B) with corresponding high signal on T2WI (red arrow). Both lesions had regressed on the MRI scan performed from July 2014.

Fig. 2 – Contrast-enhanced CT scan from February 2013 (A) demonstrated low-attenuation lesion in spleen (yellow arrow), spiculated mass in right lung (red arrow) likely representing the primary lesion, and further nodular metastasis in bilateral lung fields (green arrow). All of above lesions had regressed on CT scan from July 2014.

discharged to community palliative care team for symptomatic management. In May 2014, patient was re-referred by the general practitioner as she had remained clinically stable despite being diagnosed with metastatic lung cancer 15 months previously. She underwent further imaging that demonstrated complete regression of the previously evident lesions (Figs. 1 and 2). Subsequently, the steroids were gradually tapered and she discontinued her dexamethasone in July 2014. She underwent further imaging at three monthly intervals and her last imaging in April 2015 still showed no evidence of recurrence.

Discussion

The differential diagnosis of mass lesions in the lungs and brain can be varied and is summarised in Table 2. The patient was afebrile with no infective or systemic symptoms and normal inflammatory markers that was against a likely diagnosis of infection, or vasculitic disorder. The CT scan did not demonstrate any significant lymphadenopathy that excluded the possibility of systemic B-cell or T-cell lymphomas, or systemic granulomatous disease such as sarcoidosis. However, primary lung and cerebral lymphomas may arise in

Table 2 – Differential diagnosis of radiological presentation of synchronous mass lesion in lungs and contrast enhancing lesions of brain.

Malignancy	Lymphomatoid granulomatosis	Infection	Vasculitis	Granulomatous diseases	Lymphoma
<ul style="list-style-type: none"> Disseminated malignancy 	<ul style="list-style-type: none"> B-cell lymphoproliferative disorder EBV-associated disorder 	<ul style="list-style-type: none"> Tuberculosis Brain abscess Fungal infection Exposure to source of infection Immunosuppression (e.g. drug, HIV) Travel to endemic region 	<ul style="list-style-type: none"> Primary angitis Wagener granulomatosis History of autoimmune disorder 	<ul style="list-style-type: none"> Sarcoidosis Vasculitis Infection History of autoimmune disorder 	<ul style="list-style-type: none"> Primary systemic B or T cell lymphoma Primary cerebral lymphoma (B-cell origin) Primary lung lymphoma (MALT)
<ul style="list-style-type: none"> Evidence of other primary tumour – lung, breast etc. Systemic symptoms Pressure symptoms Normal inflammatory markers 	<ul style="list-style-type: none"> Evidence of EBV infection – positive EBV serology Multi-organ involvement (lungs, skin) 	<ul style="list-style-type: none"> Pyrexia Systemic symptoms Raised inflammatory markers Positive blood cultures 	<ul style="list-style-type: none"> Systemic symptoms Pyrexia Multi-organ involvement – involvement of skin, sinuses, orbit, kidneys Positive auto-antibodies (ANCA) 	<ul style="list-style-type: none"> Presence of bilateral hilar lymphadenopathy Systemic symptoms Multi-organ involvement (e.g. skin, eyes) 	<ul style="list-style-type: none"> Presence of lymphadenopathy and systemic symptoms in high grade primary systemic lymphomas Primary lung and cerebral lymphomas remain localised to site of origin

EBV – Epstein–Barr virus; ANCA – anti-neutrophil cytoplasmic antibody; MALT – mucosal associated lymphoid tissue.

the absence of significant lymphadenopathy. Primary lung lymphoma usually falls within the spectrum of extra-nodal marginal-zone lymphoid tissue (MALT) group of neoplasms that are relatively indolent and unlikely to metastasise to other distant sites, particularly brain. Similarly, primary cerebral lymphomas, although characterised by aggressive modes of progression, are unlikely to spread beyond their site of origin. The other diagnostic possibility would be the rare and uncommon disorder pulmonary lymphomatoid-granulomatosis (P-LyG) classified by the World Health Organization (WHO) under the generic heading of B cell proliferations of uncertain malignant potential and in the family of EBV-associated B cell lymphomas. In our patient there was serological evidence (positive EBV-IgG) of previous EBV exposure. Lung is the typical organ involved in P-LyG with synchronous involvement of the skin (25–50%) and central nervous system (CNS) in up to 30% of patients.^{1,2}

The diagnosis of primary lung cancer with brain metastasis in our patient was made in controlled multi-disciplinary environment comprised of oncologists, radiologists, respiratory physicians, and pathologists. Patient was commenced on steroids for symptomatic relief and discharged to community palliative care services with terminal prognosis of likely few months. However, the subsequent unexpected outcome raised strong arguments about the validity of the original diagnosis. Did this represent true SR of lung cancer with brain metastasis?

The concept of SR of malignancy was proposed by Cole et al. (1976) which includes a complete or partial, temporary or permanent disappearance of all or at least some relevant parameters of a soundly diagnosed malignant disease without any medical treatment or with treatment that is considered inadequate to produce the resulting regression.³ However, SR is extremely rare phenomenon with an estimated incidence of 1 in 60,000 to 100,000 cases.⁴ The phenomenon of SR of lung cancer has been reported previously and Kappauf et al. (1997), reviewed 15 cases of SR of lung cancer.⁵ Immune-modulatory mechanisms are likely to play a predominant role in mediating SR of malignant lesions.^{6–8} Intriguingly, there are no published case reports of SR of lung cancer with brain metastasis.

In our opinion the probability of steroid-associated SR of lung cancer with brain metastasis is much lower compared to alternative diagnostic possibilities such as vasculitic or granulomatous disorder, and in particular P-LyG. The possibility of immune-modulatory mechanisms playing a possible role in this particular case cannot be ignored as there was evidence of immunosuppression with low lymphocyte count at presentation related to chronic methotrexate therapy. Subsequently, methotrexate was discontinued that was associated with normalisation of lymphocyte and immunoglobulin levels and probable restoration of immune-competent state. Indeed, there have been several reports of P-LyG arising on background of immunosuppressive therapy (e.g. methotrexate) regressing after withdrawal of the immune-suppression.⁹ However, there have been no published case reports of steroid-induced regression of lesions in the presence of CNS involvement. Similarly, corticosteroids may induce remission in other lymphoproliferative disorders but the possibility of any responses observed in the presence of CNS involvement are likely to be short-lived and most patients will eventually

require cytotoxic chemotherapy for inducing durable remission. Therefore, the unexpected outcome of this patient could be described as a “unique” event, but unfortunately the absence of histopathological confirmation clouds the development of this “unique” event and explanation of probable underlying mechanisms remains speculative.

The ethical integrity of the original MDT decision for not pursuing a biopsy for this patient cannot be questioned as it was based on the understanding of avoiding unnecessary invasive intervention if it was unlikely to alter the overall management and prognosis. However, this case also highlights the inherent limitations and potential pitfalls of using isolated radiological evaluation for diagnosing malignancy.

The implications of such an unexpected outcome from patient's perspective cannot be underestimated and can be described nothing short of an emotional “roller-coaster”. The importance of pursuing aggressive histopathological confirmation in these circumstances cannot be overemphasised, particularly when faced with a probable diagnosis of malignant disorder which will almost certainly represent one of the biggest life-changing events most patients will ever experience during their life-time. Finally, this case demonstrates the complexity of modern medical diagnosis and decision-making and the varying “shades of grey” that may be encountered in routine clinical practice.

Conflicts of interest

The authors have none to declare.

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