CASE REPORT

Diminution of falsely elevated tumour markers following immunosuppression for systemic lupus erythematosus with neurological involvement

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SUMMARY

We describe the case of a patient with a long history of undifferentiated connective tissue disease who developed headache, ataxia and orofacial dyskinesia attributed to a diagnosis of systemic lupus erythematosus (SLE). Gross elevation of the concentration of several plasma tumour markers (CEA, CA-125, CA19-9, CA15-3) was detected in the absence of malignancy. These markers fell significantly within a month of starting immunosuppressive therapy alongside clinical improvement. Caution should be taken in the interpretation of plasma tumour markers in patients with connective tissue disease.

BACKGROUND

Movement disorders may be associated with several distinct pathologies including systemic lupus erythematosus (SLE) and malignancy.¹ As part of the investigative work up of patients presenting with movement disorders, physicians may therefore request tumour markers. These are used in clinical practice to aid in diagnosis, screening or follow-up of patients with solid organ malignancy including carcinoma of the breast, ovary, bowel, prostate and pancreas.² However, false-positive results may be yielded through different pathophysiological mechanisms³ and have been observed in a wide range of non-malignant conditions such as rheumatic disease, thyroid disease, hepatitis and sarcoidosis. In autoimmune disease, patients' endogenous antibody can interfere with the immunoassay used to detect the antigen of interest, giving false results.

CASE PRESENTATION

We report the case of a 71-year-old woman followed up in the local rheumatology service since 2007 with undifferentiated connective tissue disease characterised by non-erosive peripheral polyarthritis, myalgia and positive serology to antinuclear antibodies (ANA), antidouble stranded DNA, anti-Ro and anti-La antibodies. Dry eyes and dry mouth symptoms were absent and the patient fulfilled only 3 of 11 American College of Rheumatology (ACR) criteria for SLE. Rheumatoid factor was intermittently detected at low titre during follow-up and anticyclic citrullinated peptide serology and other extractable nuclear antigens were negative. Her musculoskeletal symptoms were treated at various times with hydroxychloroquine, methotrexate, non-steroidal anti-inflammatory drugs and courses of corticosteroids.

Her medical history was relevant for hypertension, hyperlipidaemia, transient ischaemic attack in 2012, vulval intraepithelial neoplasia and chronic obstructive pulmonary disease.

At review in July 2015, arthritis had deteriorated with elevation of antidouble stranded antibody levels at 67 iu/mL (reference range 0–10 iu/mL) noted from blood tests in March 2015, although complement levels were normal (C3 1.30 g/L, C4 0.22 g/L). This prompted the start of methotrexate building up to a dose of 15 mg weekly. In September, the patient experienced an episode of amaurosis fugax and subsequently was admitted to hospital, with orofacial dyskinesia and ataxia associated with headache. Nystagmus and slurred speech were noted intermittently. Symptoms were initially episodic but became more persistent over the following few weeks with daily headache and ataxia hindering mobility such that the patient required the assistance of a walking frame and two attendants. Methotrexate therapy was withheld at this time due to concerns that her presentation might represent an adverse drug reaction.

INVESTIGATIONS

MRI brain showed only minor ischaemic change with no cerebellar pathology and MR angiography showed evidence of neither vertebral arterial dissection nor significant carotid stenosis. Cerebrospinal fluid (CSF) analysis showed no increase in leucocytes, with normal protein (0.36 g/L) and an increase in IgG (0.04 g/L, reference range <0.026 g/L), but no oligoclonal bands. A polyclonal rise in serum IgG was found (18 g/L, reference range 6–16 g/L). Full blood count, urea and electrolytes, liver enzymes and complement levels were within normal limits, C reactive protein was elevated (38 mg/L, reference range <10 mg/L). IgG anticardiolipin antibody was minimally elevated (11 iu/mL, reference range 0–10 iu/mL) but IgM antibody and anti-β₂ glycoprotein antibody levels were not increased. Lupus anticoagulant was negative. Antidouble stranded DNA antibody was measured at 54 iu/mL (reference range 0–15 iu/mL).

In the absence of a demonstrable cause for this patient's symptoms on brain imaging or CSF analysis, a number of diagnoses were considered. The patient was given a trial of therapy for basilar migraine (topiramate then flunarizine), without improvement. Her symptoms were not thought to be due to a lupus-related thrombotic episode, given the gradual onset and fluctuating course and the

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negative antiphospholipid antibodies. In addition, the patient was already treated with clopidogrel following a previous transient ischaemic attack. As she was in sinus rhythm, clopidogrel was continued rather than starting anticoagulation.

The possibility of a paraneoplastic movement disorder was considered prompting tumour markers to be measured. These were grossly elevated—CEA 33.8 µg/L (reference range 0–8 µg/L), CA15-3 448 µ/mL (reference range 0–38 µ/mL), CA-125 2660 kµ/L (reference range 0–35 kµ/L) and CA19-9 2920 µ/mL (reference range 0–37 µ/mL). However, thorough physical examination, gastroscopy and whole body CT scan showed evidence of neither malignancy nor other significant pathology apart from coronary artery calcification. Furthermore, anti-Purkinje cell antibodies including anti-Yo and anti-Hu antibodies were not detected.

TREATMENT

In the presence of neurological involvement, ACR and Systemic Lupus Collaborating Clinics criteria for a diagnosis of SLE were met (arthritis, neurological involvement, leucopenia, positive ANA serology, positive antidouble-stranded DNA serology). The patient was then treated with high-dose corticosteroids (prednisolone 80 mg daily) for central nervous system with a gradual improvement in her clinical condition.

OUTCOME AND FOLLOW-UP

The headache reduced in severity and frequency, speech returned to normal and the patient was able to mobilise unassisted. The dose of prednisolone was tapered accordingly. Tumour markers were repeated a month after the previous blood test and showed significant reduction in all markers (table 1)—CEA 2.5 µg/L, CA15-3 89 µ/mL, CA-125 23 kµ/L, CA19-9 260 µ/mL (CEA and CA-125 both within the normal range). CRP levels also returned to normal. Antidouble-stranded DNA antibody levels (table 2) fell from 52 iu/mL to 25 iu/mL after 2 months of steroid treatment (reference range 0–15 iu/mL). Complement levels remained within the normal range.

DISCUSSION

The tumour markers in this report are detected in our laboratory, using an immunometric ELISA assay. A solid phase-coated antibody is attached to an assay plate and the sample containing the tumour antigen of interest added. An enzyme-linked murine monoclonal antibody is then added, which binds specifically to an epitope on the bound antigen, such that the antigen is held between the solid phase capture antibody and enzyme-linked signal antibody ('sandwich' ELISA). Following addition of an enzyme substrate, quantification of the tumour antigen occurs using chemiluminescent imaging. Interference from endogenous antibodies may affect 'sandwich' immunoassays through a number of mechanisms.⁴ The endogenous antibody may mimic

Table 1 Tumour marker concentrations before and 1 month after the start of corticosteroids

Tumour marker (units)	At time of CNS presentation	One month after starting corticosteroids	Reference range
CEA (µg/L)	33.8	2.5	0–8
CA15-3 (µ/mL)	448	89	0–38
CA-125 (kµ/L)	2660	23	0–35
CA19-9 (µ/mL)	2920	260	0–37

CNS, central nervous system.

Table 2 Antidouble stranded antibody, complement and C reactive protein levels: 6 months prior to CNS involvement (time of deteriorating arthritis), and before and 1 month after starting corticosteroids

	Six months prior to CNS presentation	At time of CNS presentation	One month after starting steroids	Reference range
Anti-ds DNA Ab (iu/mL)	67	54	25	0–10
Complement C3 (g/L)	1.30	1.70	1.70	0.75–1.65
Complement C4 (g/L)	0.22	0.24	0.26	0.14–0.54
CRP (mg/L)	7	38	<7	<10

CNS, central nervous system; CRP, C reactive protein.

the antigen of interest or the signal antibody (or both) or it may bind the tumour antigen-signal antibody complex. Endogenous antibody may bind the capture antibody and simultaneously react with the signal antibody, providing a falsely elevated measurement of the tumour antigen.

Elevated plasma concentrations of tumour markers have previously been described in patients with rheumatic disease, such as rheumatoid arthritis (RA) (even in controlled disease),^{5–6} systemic sclerosis and SLE. However, false elevations of tumour markers tend to be modest in benign disease.⁷ For instance, a rise of CA19-9 >1000 µ/mL has a specificity of 99.8% for pancreatic carcinoma.⁸ False elevation of CA-125 has previously been noted in the presence of heterophilic antibodies cross-linking the antibody used in the immunoassay, with removal of the heterophilic antibody leading to normalisation of CA-125 levels.^{9–10} We speculate that the same mechanism may have occurred in our patient, whereby an endogenous heterophile antibody has bridged the capture and the signal antibodies in the assay, although the precise antigenic target of the human antimouse antibody is unknown.

Some tumour antigens are expressed on inflammatory cells and have carbohydrate motifs involved in cell adhesion. It has been postulated that these antigens may also be involved in cell adhesion in the synovium of patients with rheumatic diseases, as tumour markers (CEA and CA19-9) have been observed to be higher than controls in serum of patients with RA.¹¹ However, the mean concentration of both markers in patients with RA in this study was less than double of controls and we feel it is unlikely that this mechanism alone could account for the gross elevation of tumour marker concentrations seen in our patient.

It is possible that variations in tumour marker concentrations in patients with autoimmune disease may occur according to the degree of disease activity present and the amount of autoantibody produced. In patients with SLE, CA-125 levels have been demonstrated to correlate with disease activity.¹² The degree of elevation of these plasma markers in our patient is unusual and may represent particularly high disease activity. SLEDAI-2000 score was 14 in our patient prior to the start of immunosuppression, indicative of active disease.¹³

SLE is a multisystem condition that may present with a variety of physical and neuropsychiatric symptoms. Neurological features are well recognised, including headache, seizures, stroke, peripheral neuropathy, cognitive dysfunction and psychosis,¹⁴ and their presence is indicative of high disease activity. Movement disorders are less commonly observed but include dystonia, chorea and ataxia.¹⁵ Immunosuppressive

therapy including corticosteroids may be indicated in the presence of neuropsychiatric features due to active disease.¹⁶ In our patient, neurological features and tumour markers both improved significantly within a month of starting corticosteroid treatment. Theoretically, correction of abnormal autoimmunity and reduction in disease activity may be responsible for the observed reduction in tumour marker concentrations. Treatment of active SLE has previously been shown to return elevated CA-125 levels to the normal range.¹⁷

To the best of our knowledge, this is the first report of false elevation of all four—CEA, CA-125, CA19-9 and CA15-3—falling with treatment of active SLE in a single patient. This case serves as a reminder that tumour marker levels can be falsely elevated in the presence of connective tissue disease particularly during periods of increased disease activity. Furthermore, it also provides evidence that concentrations of these markers may fall with treatment of SLE. This should be taken into consideration when requesting and interpreting tumour markers in patients with connective tissue disease, and in the follow-up of patients in whom malignancy and autoimmune disease coexist. For instance, in women with SLE treated for ovarian carcinoma and followed up with serial CA-125 measurements, fluctuation of CA-125 concentrations may reflect SLE activity as well as response to treatment of the malignancy.

Learning points

- ▶ Tumour markers may be falsely elevated in rheumatic disease, particularly when disease activity is high.
- ▶ Tumour marker concentrations may fall with immunosuppressive therapy given for rheumatic disease.
- ▶ Clinicians should interpret tumour marker results with caution in patients with rheumatic disease.

Contributors Both authors were involved in the subject's clinical care. JB wrote the report and MR helped review the manuscript. Both authors read and reviewed the final manuscript. Written patient consent was obtained prior to submission of the manuscript.

Competing interests None declared.

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