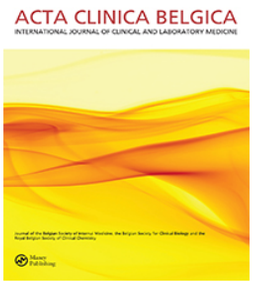

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Case Report

How far to investigate presumed psychosomatic symptoms: Lessons from a particular case…

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We describe a 43-year-old patient with subacute appearance of neurological and atypical complaints of anergia, anorexia and weight loss six months earlier. In spite of several admissions in different hospitals, no underlying somatic cause could be found and he was admitted to a psychiatric hospital with a tentative diagnosis of major depressive disorder. Subsequently, he was referred to the unit of medically unexplained physical symptoms within the department of general internal medicine for assessment by the psychiatrist, involved in this programme. Based on clinical suspicion and red flag symptoms such as involuntary weight loss, a broader internal medicine reassessment, including FDG whole-body PET–CT was requested. Neurological clinical exam showed minor deviations, but neither brain imaging nor a lumbar puncture were contributory. However, FDG PET–CT revealed abnormal moderately to intensely FDG positive lymph nodes in the retroperitoneum. Laparoscopic lymph node biopsy indicated germ cell tumour metastasis. Anti-NMDA antibody positivity allowed a diagnosis of paraneoplastic anti-NMDA encephalitis. Treatment of the underlying disease, a pure seminoma stadium II, consisting of orchidectomy and chemotherapy, resulted in a spectacular regression of 'psychosomatic' symptoms with long-term ability to return to work, and documented disappearance of the anti-NMDA antibody response.

Keywords: Paraneoplastic encephalitis, Anti-NMDA-receptor, Seminoma, Psychosomatic presentation

Case report

In November 2013, a 43-year-old man consulted the psychiatrist within the department of general internal medicine for medically unexplained physical symptoms (MUPS) for a second opinion. His personal medical history was uneventful until May 2013. The family history was also negative. His complaints started with subacute appearance of unbalanced gait, vertigo, instability and coordination problems. During the following weeks, he also developed nausea, vomiting and extreme exhaustion.

Six months before intake in our unit, the general practitioner referred him to the emergency room where he was diagnosed with a flu-like syndrome. The complaints persisted and in the following months consultations with different subdisciplines, including a laryngologist, neurologist and endocrinologist did not result in a clear explanation.

A consultation in August 2013, when symptoms were ongoing for four months, at the neurology department in our hospital could not confirm a central neurological aetiology, either. However, at that time the patient presented with severe hyperventilation, introducing inconsistencies into the clinical examination. A possible non-organic aetiology was discussed with patient and partner. Further examination was proposed, such as repeating brain MRI and lumbar puncture, but were cancelled, since the patient was at that point admitted to a psychiatric hospital, with a suspicion of an underlying major depressive disorder, in spite of the absence of any prior history of psychiatric disorders. No significant symptomatic improvement was observed with a duloxetine trial treatment.

His partner insisted on a second opinion and two months after admission to the psychiatric hospital, the patient was referred to our department for assessment of MUPS, as multiple investigations remained negative suggestive of functional disorder.

The evaluation by the psychiatrist, involved in the diagnostic path for MUPS, however was not suggestive of psychiatric illness and pointed to a number of atypical and even red flag symptoms. These included the subacute vertigo, instability and coordination problems (especially of

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the left hemisoma). These neurological symptoms already persisted for six months and were associated with nausea and vomiting, asthenia, fatigue and a weight loss of +/−10 kg. After interdisciplinary consultation, we decided to admit the patient for observation and further examinations in the department for general internal medicine.

At intake, important anxiety and severe hyperventilation were present. However, clinical neurologic examination revealed minor abnormalities, including an uncertain and broad-based gait, a positive Romberg test to the left, a very discrete nystagmus and ataxia in the left knee-heel test. A new MRI of the brain and lumbar puncture were executed to exclude a fossa posterior lesion or inflammatory disease.

Biochemical screening including inflammatory parameters, hormonal, viral and autoimmune serology, was negative.

Because of the presence of red flag symptoms, especially the involuntary weight loss and asthenia, a FDG PET–CT scan (Fluoro ^{18}-deoxyglucose Positron emission tomography–computed tomography) was performed up front in order to exclude underlying inflammatory or malignant disease. This revealed peri-centimetric lymph nodes situated in the left inter aorta-caval and para-aortic region and at the aortic bifurcation, and some infra-centimetric lymph nodes para-aortic, that all proved to have intense FDG uptake (Fig. 1).

This imaging was considered suggestive for lymphoproliferative disease. Taking into account the initial clinical presentation, a paraneoplastic encephalitis was hypothesised, for which antineural antibodies were screened.

A second lumbar puncture and bone marrow aspirate did not reveal additional clues to invasive lymphoma. Meanwhile, serologic screening allowed for exclusion of alternative diagnoses as *Bartonella henselae*, *Borrelia burgdorferi* or *Toxoplasma gondii* infection and a tuberculin skin test was negative. To confirm the hypothesis of lymphoma, a lymph node biopsy was considered the necessary next step. However, in the case discussion with abdominal surgery, there was an initial reluctance to perform either an open or laparoscopic procedure, because of doubts on the significance and the causal relationship of the PET–CT findings with the neurological symptoms, consisting of only discrete clinical abnormalities. As an alternative, a watch-and-wait approach, repeating PET–CT after 2–3 months, with careful clinical follow-up, was proposed.

This was largely discussed and the patient and family were informed on the risks and benefits of both approaches. Finally, because of the protracted diagnostic uncertainty and the important impact on quality of life, and in mutual consent with the patient, a laparoscopic biopsy was performed at the end of December, eight months after appearance of symptoms. Pathologic examination allowed exclusion of lymphoma but demonstrated atypical cells, identified as a metastatic localisation of a germ cell tumour, most probably a seminoma.

Initial clinical testicular examination was normal and there was no abnormal FDG-uptake in the testis. A subsequent ultrasound examination of the testes showed a suspicious area in the right testis. A radical orchiectomy was immediately performed. Anatomopathologic examination revealed only a zone of necrosis and scarring with a focus of neoplastic cells whose immunological characteristics, expression of SALL4, refer to a seminoma undergoing burn out changes. Tumor markers ß-HCG and æ-FP were negative, adding on to the diagnosis of a stage II pure seminoma (Fig. 2).

The patient was transferred to the oncology department, where a systemic chemotherapy with three cycles (every three weeks) of bleomycine (30 mg fixe dose at D1-D8-D15), etoposide(100 mg/m²D1-2-3-4-5) and cisplatinum (20 mg/m²D1-2-3-4-5)) was initiated because of the presence of a stage II seminoma. At one year

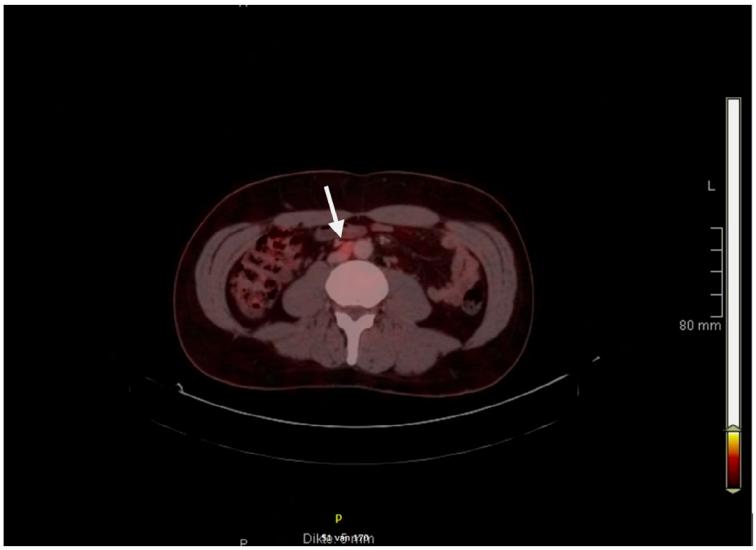
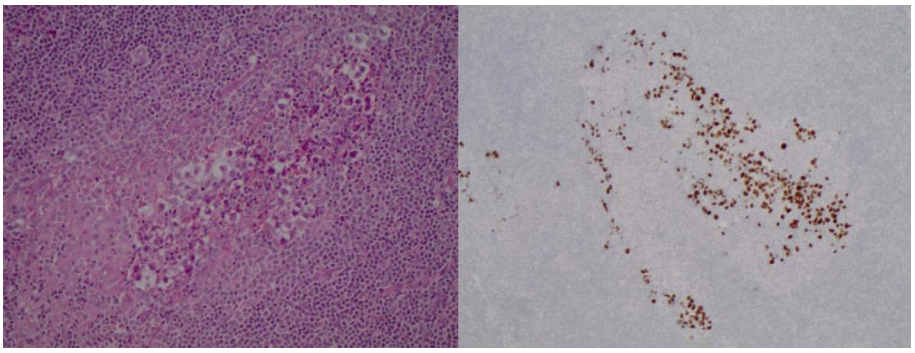


Figure 1 PET scan revealing intense PET positive lymph nodes in the retroperitoneum (arrow).



HE x 20 SALL4 x 20

Figure 2 Histopathology of the testis: a focus of atypical cells was present amid necrosis and fibrosis with positivity after SALL4 immunostaining revealing a positive nuclear staining of the neoplastic cells pointing out the definitive diagnosis of seminoma.

post-treatment remission could be confirmed with simultaneous spectacular regression of neurological symptoms. Patient is currently active and working again. He regained 11 kg since the treatment.

As an explanation for the neurologic symptoms, paraneoplastic encephalitis was suspected but could not be confirmed by MRI, nor by first line paraneoplastic antibody screening (anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-amphi, anti-CV2, anti-Ma1 and anti-Ma2), which all turned out negative. A subsequent screening for anti-NMDA (N-methyl-D-aspartate) receptor antibodies however was positive, confirming the diagnosis of anti-NMDA receptor encephalitis. A long-term reassessment of anti-NMDA receptor antibodies two years after treatment of the underlying seminoma with remission was negative, strengthening our hypothesis of paraneoplastic neuropsychiatric symptoms. However, significant despair and frustration may have originated from the lack of diagnosis in the first 6–8 months of the syndrome, reinforcing the subjective perception and impact of the paraneoplastic neuropsychiatric symptoms.

Discussion

How far to investigate presumed psychosomatic symptoms?

In clinical practice, it remains a major challenge for the physician, both in primary care and in general internal medicine and other disciplines, to recognise markers of underlying severe disease within any constellation of general, often vague, and in the majority of the cases, benign complaints, albeit with significant impact on daytime functioning and health-related quality of life.

These clinical situations are characterised by a negative first or even second-line evaluation and the inability to link patient symptoms to any underlying well described or known nosologic entity with specific diagnostic testing. Red flag symptoms and signs constitute an important trigger, defining the threshold to proceed to more in-depth screening. In this case report, the important and involuntary weight loss, the atypical presentation of chronic fatigue, the absence of any prior history of psychiatric disorders and the lack of vulnerability to develop MUPS were picked up by a psychiatrist, embedded into a department of general internal medicine. This allowed for low threshold interaction between different specialties, triggering further diagnostic testing. This underscores the importance of multi-, and, preferably, interdisciplinarity in the approach of MUPS.

Indication for PET or PET/CT

The PET scan clearly contributed to the final diagnosis in this particular case. PET guidelines focus mainly on the diagnosis and assessment of extent of disease (staging) at time of initial diagnosis or the detection of residual or recurrent disease, mainly in malignancy but also in a number of infectious or inflammatory conditions. Literature offers little guidance as to how to use PET in any setting of unexplained symptoms, even in classic syndromes such as fever of unknown origin (FUO) or unexplained weight loss[1,2] These conditions are defined by negative first-line investigations. PET, early in the further diagnostic algorithm, probably shortens diagnostic delays. In FUO a low threshold for PET has been advocated, resulting in a significant diagnostic yield. Meller *et al.*[1], show that the PET scan in second line contributed to the final diagnosis in 2569% of the patients with FUO. This strategy could be expanded to a larger spectrum of unexplained red flag symptoms such as unexplained weight loss and atypical presentations. The latter requires a high degree of suspicion of an underlying somatic cause, which depends on the integrated clinical assessment of the individual case. This exemplifies where medicine, dealing with probabilities, turns into an art (Wiliam Osler).

High negative and positive predictive values should be taken into account. With high negative predictive value, a negative PET scan will incline towards watchful waiting, whereas because of high positive predictive value, a positive PET scan, revealing FDG positive lymph nodes should trigger the next step of obtaining relevant samples for histologic evidence. Especially in oncology these high predictive values are well described.[3,4] But also in a prospective study in FUO, estimated diagnostic accuracy, sensitivity and specificity of ^{18}F-FDG-PET/CT for detecting underlying disease were 90.5, 93.8 and 80%, respectively.[5]

Burned-out tumours

Burned-out testicular tumours are defined as testicular germ cell tumours that regress spontaneously but manifest by metastatic spread. Primary extragonadal germ cell tumours constitute 3 to 5% of all germ cell tumours. More than 60% of these tumours are seminomas arising in the anterior mediastinum and retroperitoneum. Investigation of the testes usually only reveals residual scarring. Retroperitoneal masses with histologic demonstration of a germ cell tumour, should always be considered a burned-out primary testicular neoplasm until proven otherwise. It appears to be beneficial to eradicate the primary focus to prevent potential relapse after chemotherapy.

Most frequently these extragonadal germ cell neoplasms reveal themselves by palpable abdominal masses or lymphadenopathy. Tumours with higher tumour burden and nonseminomatous histology in metastases, especially choriocarcinoma, have a worse prognosis.

Rare associations of spontaneous tumour regression and paraneoplastic syndromes have been described in the literature, especially in small cell lung cancer. Case reports support the hypothesis that anti-Hu neurologic syndromes are the consequence of a misdirected immune response to small cell tumours. This could also be the case in other cancers where an efficient T cell response could destroy the tumour but by its unfocused activation attacks other organs.[6,7]

Paraneoplastic encephalitis

Encephalitis, especially in young people, is most likely to be of viral origin. However, if symptoms persist, lumbar puncture and screening for infectious agents are negative and MRI of the brain is inconclusive, a whole body CT and/or PET imaging and autoimmune serology to exclude a paraneoplastic manifestation should be considered.[8,9]

Most cases of paraneoplastic encephalitis in men of younger age are associated with testicular tumours and present positive anti-Ma2 antibodies. Treating the underlying disease can lead to substantial improvement in symptoms.

Anti-NMDA receptor encephalitis can be paraneoplastic as well as non-paraneoplastic. A case series has been described in female patients with teratoma. In most cases MRI is unrevealing. Until present, very limited neuropathological data are available but abnormalities seem to be non-specific. One of the possible explanations is a reversible defect in the number of NMDA receptors.[10,11]

NMDA receptors are ligand-gated cation channels with a crucial role in synaptic transmission and plasticity.

The clinical presentation of psychosis-like symptoms, seizures, abnormal movements and autonomic disturbances is highly characteristic of NMDA-receptor antibody encephalitis.[12]

Of patients with anti-NMDA-receptor encephalitis, many were initially seen by psychiatrists or admitted to psychiatric centres but subsequently developed symptoms requiring multidisciplinary care. Approximately 60% of the patients have an underlying malignant disease.

Anti-NMDA-receptor encephalitis represents a new category of immune-mediated disorder that is often paraneoplastic, treatable and can be diagnosed serologically.

Conclusion

Atypical presentations, especially in the presence of red flag symptoms and/or signs, merit a thorough clinical assessment. A PET CT should be considered in an early phase following an inconclusive first round of classical investigations, in view of high negative and positive predictive values. This case illustrates the importance of a multi- or even interdisciplinary approach and continued empathic and inquisitive approach of patients with MUPS, even (and maybe especially) in the presence of a predominantly psychogenic clinical presentation.

Contributors

MDS provided, collected and analysed the data, wrote the article in whole, revised the article. SR, AM and MP provided part of the data, revised the article. DV analysed the data, wrote the article in part, revised the article.

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