Isolated Myelopathy in Occult Breast Carcinoma with Negative Paraneoplastic Antibodies: A Case Report of a Rare Condition

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Abstract: Isolated paraneoplastic myelopathy (IPM) is a rare neurological manifestation of systemic cancer and represents an intermediate-risk phenotype of disease according to the diagnostic criteria for Paraneoplastic Neurologic Syndromes (PNS). Here, we present the case of a 47-year-old woman who developed subacute cervical myelopathy and was then diagnosed with breast cancer. Through this lens, we provide a discussion of current literature on IPM. Over four months, our patient developed progressive tetraparesis, hypoesthesia with C3 level, and urinary retention. The first MRI was negative, but a four-month-control MRI showed a T2-hyperintense spinal lesion (C2–C7 and T2–T4). Cerebrospinal fluid (CSF) analysis was normal. Infective and autoimmune screening, including onconeural, anti-MOG, and aquaporin-4 antibodies, was unremarkable. The total-body CT scan was negative, but total-body PET-CT scan evidenced an enlarged axillary lymph node, with the detection of breast cancer cells at fine-needle aspiration. Despite negative mammography, a breast MRI confirmed a mammary nodule, which was removed, and a ductal infiltrating breast carcinoma diagnosis was made. Her neurological condition partially improved after steroid therapy. Our final diagnosis was probable IPM, according to PNS criteria. This rare condition affects most frequently middle-aged women and is often associated with breast and lung cancer, even if two-thirds of patients’ cancer diagnosis is subsequent to the onset of neurological deficits. Clinical presentation is often subtle, and CSF analysis, neuroimaging, and onconeural autoantibodies could be negative or non-specific. However, if the suspect of paraneoplastic disease is strong, cancer should be searched thoroughly since early diagnosis and treatment are associated with a better outcome.

Keywords: isolated paraneoplastic myelopathy; inflammatory myelopathy; paraneoplastic syndrome; breast cancer; autoantibodies; myelitis

1. Introduction

Pathologies that affect the spinal cord are multiple and diverse. Although multiple sclerosis (MS) represents the more common cause of inflammatory myelopathy, other inflammatory conditions include aquaporin-4 (AQP4) IgG-positive neuromyelitis optica spectrum disorders (AQP4 + NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) [1,2]. A myelitis is a spinal cord inflammation with a cross-sectional area entirely or partially involved, hence being defined as transverse or partial myelitis [3]. However, an increasing number of alternative etiologies must now be considered in the diagnostic work-up of myelitis patients. In addition to trauma, common etiologies of myelopathy include infectious, metabolic, neoplastic, vascular, and hereditary-degenerative diseases [3]. Rarely a paraneoplastic genesis can be recognized [4]. Paraneoplastic myelopathy, resulting in a rapidly progressive spastic paresis...
with or without sphincteric dysfunction, usually occurs in association with the involve-
ment of other areas of the nervous system, such as the brain, peripheral nerves, and optic
nerves [4]. Different neuronal nuclear and cytoplasmic autoantibodies may be detected
in serum or cerebrospinal fluid (CSF). The most common are glial fibrillary acidic protein
(GFAP), amphiphysin, collapsin response mediator protein-5 (CRMP-5), antineuronal nu-
clear antibodies type 1 and 2 (ANNA-1 or anti-Hu, and ANNA-2 or anti-Ri), Purkinje cell
cytoplasmic autoantibody type-1 (PCA1 or anti-Yo), glycine receptor, and glutamic acid
decarboxylase-65 (GAD-65) antibodies [3,5,6]. In diagnosing a suspected paraneoplastic
genesis, serum, and CSF testing should be complementary [5]. Due to the rarity of paraneo-
plastic syndromes, the differential diagnosis may be challenging, particularly of isolated
spinal cord lesions (isolated paraneoplastic myelitis (IPM)) [4]. In particular, a solitary
spinal cord lesion may be difficult to place in a specific syndrome due to clinical and radi-
ological overlapping features. Moreover, non-inflammatory diseases may sometimes mimic
inflammatory diseases [3]. The more common IPM associated-antibodies are amphiphysin
and CRMP-5 antibodies [7]. However, even more rarely, no specific onconeural or surface
auto-antibodies are seen, producing the diagnosis even more challenging. Specific diag-
nostic criteria for paraneoplastic syndromes are available to help the clinician [8]. IPM
without paraneoplastic antibodies is extremely rare in the current literature. The paraneo-
plastic origin should be considered in the presence of suggestive MRI and the exclusion
of any other differential diagnoses such as infections, metabolic disorders, autoimmune
non-paraneoplastic diseases, tumors, and neurodegenerative diseases disease.

Here, we further present the case of a woman diagnosed with IPM in the context of
occult breast carcinoma with negative paraneoplastic antibodies and review the red flag or
pitfalls that can help the diagnosis.

2. Case Report

A 47-year-old Moroccan woman developed a progressive walking difficulty associated
with paresthesia over four months, first in her hands, then in the lower limbs and trunk.
Her medical history included hypertension, moderate mitral insufficiency, allergic asthma,
chronic migraine, and bilateral carpal tunnel syndrome treated with surgical decompression.
Because of the progression of symptoms, she was admitted to the Neurological department
of her hometown hospital. She underwent a total spinal MRI, which was negative for
myelopathy and only showed C5–C6, C6–C7, and L5-S1 disc protrusions without radic-
ular compression. A lumbar puncture with CSF examination revealed slight pleocytosis
(33 cells/µL, mainly monocytes) with normal proteins. Electro-neuro-myography (ENG-
EMG) of the four limbs was normal except for mild bilateral carpal tunnel syndrome. Motor
and somatosensory evoked potentials in the lower limbs showed bilateral damage of the
corticospinal and somatosensory pathways. She was dismissed from the hospital with oral
steroid therapy in the hypothesis of cervical-lumbar discopathy. No improvement was
observed with the treatment.

In the next month, her condition progressively worsened, with a cranial extension
of the sensory symptoms and a worsening in walking. For this reason, a new admission
in our Neurological department was proposed. The neurological examination revealed
a moderate tetraparesis, mainly proximal, a tactile epicritic sensory loss with C3 level
associated with burning paresthesia in the limbs, a proprioceptive sensory loss with distal
loss of joint position sense, index-nose and hell-shin maneuver deteriorating with eye
closing with sensory ataxia with a wide base and reeling gait and positive Romberg sign;
reduced tendon reflexes; right Babinski sign, and urinary retention. A new spinal MRI
showed a T2-hyperintense lesion from C2 to C7 and T2 to T4, mainly involving the dorsal
columns without contrast enhancement (Figure 1). The brain MRI was normal.
Figure 1. Sagittal spinal cord MRI T2-weighted image showing a longitudinally extensive T2 signal abnormality from C2 to C7 (star) with spinal cord swelling particularly at C3 levels in the dorsal column. After administration of gadolinium no pathological contrast enhancement is appreciated. Radiological findings are consistent with inflammatory myelitis.

Lumbar puncture was repeated and CSF examination showed mild raised protein level (66 mg/dL) with slight pleocytosis (17 cells/μL), increased intrathecal immunoglobulins synthesis indices (Kappa Free light chain Index of 16.5, CSF IgG 8.92 mg/dL, Link’s Index 0.5), and the presence of a type 3 pattern at isoelectrofocusing and immunoblotting. Routine blood investigations (e.g., blood count, metabolic profile including vitamin B12) showed no abnormality. The infective screening (including syphilis) was unremarkable. Antibodies directed toward VGCC, VGKC, GluR3 A/B, basal ganglia, LGI1, NMDAr, Caspr2, AMPA1 AMPA2, GABA B1 tested negative. Likewise, serum and CSF paraneoplastic antibodies (amphiphysin, GAD, Ri, CRMP-5, Hu, Yo, Ma1, Ma2, and anti-MOG, and AQP4) were not found. A total-body CT scan and mammography were normal. A whole-body PET scan revealed an enlarged axillary lymph node [Figure 2], so fine-needle aspiration was performed, and breast cancer cells were detected.

Finally, a mammal MRI confirmed the presence of a 1 cm nodule in the upper-left quadrant, so the patient underwent an excisional biopsy, which confirmed ductal infiltrating breast carcinoma, hormone-receptor-positive. Quadrantectomy was performed, and adjuvant radiotherapy and hormone therapy were undertaken. After carefully excluding neoplastic, metabolic, infective, and autoimmune causes of myelopathy, our final diagnosis was probable paraneoplastic isolated myelitis with negative paraneoplastic antibodies, according to the Paraneoplastic Neurologic Syndrome (PNS)-Care Score [8] (Figure 3).

Consequently, high-dose intravenous steroid treatment (methylprednisolone 1 g for five days) was started, without relevant improvement, even if a new spine MRI performed two weeks after steroid therapy showed a slight reduction of the lesion in C2–C7 and T2–T4. Despite cancer treatment and physical rehabilitation, at follow-up she still reported debilitating positive sensory symptoms in the four limbs, unresponsive to medications (therapeutic attempts have been made with pregabalin 300 mg/die, venlafaxine 225 mg/die, duloxetine 60 mg/die, amitriptyline 30 mg/die, carbamazepine 400 mg/die). Moreover, the ability to walk remained impaired. Subsequently, a cycle of intravenous immunoglobulins (400 mg/kg for five days) was carried out with poor benefit. At the final follow-up visit, we observed unstable standing, possible only with double support, paretoataxic gait for
just a few steps, and sensory loss with C3 level with burning paresthesia in the limbs. She continues oncologic follow-up.

![Whole-body PET scan revealing an enlarged axillary lymph node (red star), with fluorodeoxyglucose hyperaccumulation](image)

No spinal cord or breast hypermetabolic foci were found. The letter correspond to axial (A), sagittal (B) and frontal (H).

**Figure 2.** Whole-body PET scan revealing an enlarged axillary lymph node (red star), with fluorodeoxyglucose hyperaccumulation (in (a) an axial image (b) a sagittal image and (c) a frontal section). No spinal cord or breast hypermetabolic foci were found. The letter correspond to axial (A), sagittal (B) and frontal (H).

**Figure 3.** The most recent diagnostic criteria for PNS defines three levels of certainty of diagnosis (possible, probable, and definite PNS) based on clinical phenotype (high risk or intermediate risk phenotype or phenotype not associated with cancer), the presence or absence of antibodies, and the type of antibodies and the presence or absence of cancer. We obtain a score ranging from 0–10 (<3 not PNS, 4–5 possible PNS, 6–7 probable PNS, >8 definite PNS). Our case scored 6, corresponding to a probable PNS. Figure created with Biorender.com (Accessed on 21 November 2022).
3. Discussion

Paraneoplastic myelopathies are a rare and generally unrecognized remote effect of cancer with immune-mediated pathogenesis [8]. They can present as isolated syndromes (optic neuritis, cerebellar syndromes, neuropathies, and myelitis) or as multifocal entities [2, 9]. In most descriptions, myelopathies are associated with other syndromes, such as paraneoplastic encephalomyelitis, polyneuropathies, or cerebellar ataxia, which help when in diagnosis [10]. IPM is very rare, and the exact incidence is unknown. According to data in the literature, approximately 60% of patients are women with a median onset age of 62 [6]. Our case is younger than previously reported in the literature. Usually, the clinical presentation of immune-mediated syndromes is acute-subacute [3]. However, both hyperacute clinical courses and progressive courses have been described in paraneoplastic myelopathies [3]. When the clinical presentation is subtle, with slow progression of motor and sensory deficits, it may mimic other conditions, such as discopathy like in our case, but also primary progressive MS or amyotrophic lateral sclerosis [3, 11]. Sometimes symptoms could fluctuate, making the differential diagnosis more challenging.

MRI is essential to demonstrate spinal cord inflammation, which is usually longitudinally extensive and symmetric, involving the lateral and dorsal columns, with or without gadolinium enhancement [3, 6]. However, it is important to note that up to half of the patients may have a negative normal MRI [7], as we first experienced in our case. Our case further enhances that MRI follow-up should be performed if the clinical presentation is consistent with spinal cord involvement. CSF examination in paraneoplastic myelopathy could be normal or, more frequently, could show signs of non-specific inflammation with mild pleocytosis (lymphocyte-monocytes) and slightly augmented proteins [5]. In approximately 30% of patients, oligoclonal bands (OB) can be detected. Our patient presented with OB pattern type 3, but pattern type 2 is more commonly reported.

In whole-body PET scans, no spinal cord hypermetabolic foci are normally observed. IPM is normally associated with lung and breast cancer [6]. Although onset and clinical evolution are variable, the prognosis is associated with severe disability, and improvement after treatment and cancer excision occur in a few cases [11]. Approximately two-thirds of patients are diagnosed with cancer after the onset of neurological symptoms, with a median time of 12 months (range 2–44) from the onset to cancer detection [6]. Several types of cancer are responsible for paraneoplastic myelitis, but the most often associated are breast and small-cell lung cancer, reflecting the higher prevalence of these tumors in the general population. The cancer diagnosis was particularly challenging in our case because the total-body CT scan and mammography were negative. The cancer was detected only with a total-body PET scan and breast MRI.

As for the immunological profile, most seropositive patients express anti-amphiphysin and anti-CRMP5 antibodies that are frequently associated with a previous history of breast, pulmonary, or ovarian cancer. On the other hand, about a quarter of IPM patients are seronegative [8, 12]. At the current state of knowledge, not all antibodies have probably been detected yet; the seropositive group could be further expanded in the future. In this immunological setting, different pathophysiological mechanisms are involved. Some antibodies are defined as “pathogenic” (e.g., AQP-4) because they can damage the spinal cord without additional mediators, while the majority of them are “non-pathogenic”, requiring the activation of a cytotoxic T-cell-mediated autoimmune response. Regardless of the mechanisms implicated, PNS are often the first presentation of an unknown malignancy; therefore, searching for antibodies is useful to diagnose an underlying disease [12]. The progress in research over the last two decades has made possible the creation of PNS diagnostic criteria, first published in 2004 [10, 13]. A recent update has been proposed to address these syndromes’ clinical, immunological, and oncological complexity [8]. Due to phenotypical heterogeneity, the term “classical syndromes” has been replaced by “high-risk phenotypes” for patients with diagnosed malignancy, and the new concept of “intermediate-risk phenotypes” has been introduced [8]. Moreover, “onconeural antibodies” have been redefined according to the risk of association with cancer: “high-risk antibodies”,

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if greater than 70%, and “intermediate risk antibodies” if between 30% and 70%. The PNS diagnosis proposes a three-levels-of-evidence classification: definite, probable, and possible. A PNS-Care-Score is calculated to define the evidence level by combining clinical phenotype, antibodies, presence or absence of malignancy, and duration of follow-up [8]. The definite diagnosis requires the presence of high- or intermediate-risk antibodies. Our case fulfilled the criteria for a probable level of evidence (score of 6), considering the intermediate-risk clinical profile, absence of antibodies, and cancer diagnosis [8]. Finally, PNS can be classified into two groups according to pathological mechanisms: in Group 1 the immune response is directed against intracellular or neuroglial proteins, while in Group 2 it addresses antigens within or close to the neuronal cell membrane [11,14]. In both clusters, detection, and treatment of the underlying cancer are critical and offer the best chance of clinical stabilization or remission. Group 2 disorders often respond to medical therapy, which involves corticosteroids, plasma exchange, or intravenous immunoglobulin G. Cyclophosphamide or rituximab may be helpful in patients who are not responsive to first-line therapy. For Group 1 disorders, treatment is still challenging because effective strategies are lacking. Although no comparative studies have been conducted yet, plasma exchange is considered as effective as intravenous immunoglobulin. Considering our patient’s clinical response to immunoglobulin and steroids, we could assume she belongs to Group 2, although negative onconeural autoantibodies make this conclusion speculative. PNS, especially Group 2, usually presents a poor prognosis, strongly influenced by underlying disease treatment and response to immunomodulatory therapy: the earlier the concurrent disorder is treated surgically or pharmacologically, the better the response to immunotherapy and the clinical outcomes. Our patient was in remission at the last follow-up visit and presented with moderate neurological disability. In PNS, death may be caused by cancer progression, a complication of oncological treatment, or systemic impairment (acute respiratory, congestive heart, or kidney failures) [15].

4. Conclusions

Our case well summarizes the possible difficulties encountered in the diagnostic process of a PNS: (1) the clinical presentation was non-specific and subtle; (2) the first MRI did not show any sign of myelopathy, which was present only at a control MRI several weeks later; (3) onconeural autoantibodies were not found; (4) cancer was not detected with first line imaging studies, but only with total-body PET scan and breast MRI. Therefore, our take-home message for the clinician is to consider IPM if any other cause of myelopathy has been excluded. If the diagnostic suspect of IPM is strong, cancer should always be searched with advanced approaches. Since the timing of the diagnosis strongly influences the prognosis, IPM should always be considered in the differential diagnosis of myelopathies, from more frequent such as MS, to more rare and other subacute neurological disorders, especially in middle-aged women.

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