

Chronic inflammatory demyelinating polyneuropathy caused by hepatocellular carcinoma

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SUMMARY

Paraneoplastic syndromes are rare abnormal endocrine or immune responses triggered by neoplasms. Chronic inflammatory demyelinating polyneuropathy (CIDP) is one such example. CIDP is an acquired, immune-mediated neuropathy affecting the peripheral nerves and nerve roots. It is associated with many types of cancers, especially haematological malignancies. We report the case of a man in his 60s who presented to the emergency department with acute symptoms of upper and lower extremity paresis and decreased sensation in the toes and tips of his fingers. Laboratory tests were normal. Electrodiagnostic studies showed diffuse motor and sensory dysfunction in all extremities; a diagnosis of CIDP was consequently made. Imaging studies showed a large left lobe liver mass. Subsequent biopsy revealed histopathological findings characteristic of hepatocellular carcinoma. After failure of medical treatment with intravenous immunoglobulin and corticosteroids, laparoscopic resection of the tumour was planned, performed and resulted in complete resolution of symptoms. At 18 months postoperatively, the patient was asymptomatic.

BACKGROUND

Paraneoplastic syndromes are a group of rare disorders that can occur in response to a neoplastic disease. They result from the secretion of specific peptides, chemokines, cytokines or hormones from tumour cells, as well as from immune cross-reactivity against tumour antigens, leading to autoimmune manifestations.¹ Neurological paraneoplastic syndromes specifically consist of a constellation of neurological symptoms that may involve the central, peripheral or autonomic nervous system.²⁻³ These pathologies are most commonly associated with breast cancers, ovarian cancers, small cell lung cancer, gynaecological cancers and lymphomas. For instance, chronic inflammatory demyelinating polyneuropathy (CIDP) is a neurological paraneoplastic syndrome that results from an autoimmune-mediated demyelinating peripheral neuropathy. CIDP is described most frequently in the context of haematological malignancies, especially Hodgkin's and non-Hodgkin's lymphomas, as well as haematological gammopathies. These syndromes usually manifest prior to the diagnosis of the primary malignancy and are frequently but not exclusively associated with neuronal antibodies.⁴⁻⁵ To the best of our knowledge, we describe the first case of complete resolution of paraneoplastic CIDP symptoms in response to radical resection of a hepatocellular carcinoma (HCC).

CASE PRESENTATION

A man in his 60s presented to the emergency department of our hospital with a 10-day history of ataxia, severe weakness in the lower and upper limbs, and decreased sensation at the tips of his fingers and toes. His symptoms were preventing him from performing activities of daily living, such as climbing stairs and handling objects. The patient started experiencing paraesthesia in his fingertips 1 year prior to his admission. He also reported a 2-month history of gradual, bilateral ascending numbness in his toes, reaching his hips. This was accompanied by progressive weakness in his shoulder muscles. The patient has a history of well-controlled diabetes, hypertension and latent tuberculosis.

On physical exam, he was found to have generalised areflexia. Decreased pinprick, vibration and position sensations were also noted. No cerebellar signs were present.

INVESTIGATIONS

Laboratory values at the time of admission showed normal sodium, potassium, calcium and magnesium concentrations. His liver function tests were within normal ranges. His creatinine level was stable from baseline (1.3) considering his chronic kidney disease in the setting of diabetes. Serum antibody analysis was positive for anti-SSA (Sjogren's Syndrome A), anti-beta-2 glycoprotein, and anti-ganglioside GD1a, GD1b and CQ1b antibodies, as well as ANA (Anti-Nuclear Antibody). On the other hand, anti-CCP (Cyclic Citrullinated Peptide), RF (Rheumatoid Factor) and C-ANCA/p-ANCA (AntiNeutrophil Cytoplasmic Antibody) were all negative.

Electrodiagnostic studies (electromyography and neurography) were performed and revealed a severe delay in the proximal and distal motor latencies in the peroneal, posterior tibial, median and ulnar nerves, along with a moderate decrease in motor conduction velocities in the upper and lower extremities bilaterally. This was accompanied by a drop in the compound muscle action potential amplitudes proximally compared with distally in the distribution of these nerves. There were no sensory responses in any of the examined nerves. Temporal dispersion was noticed in the median nerves. Overall, the clinical picture, laboratory findings and electrodiagnostic studies supported a diagnosis of CIDP.

DIFFERENTIAL DIAGNOSIS

The patient was then referred to the rheumatology clinic to rule out possible rheumatological or



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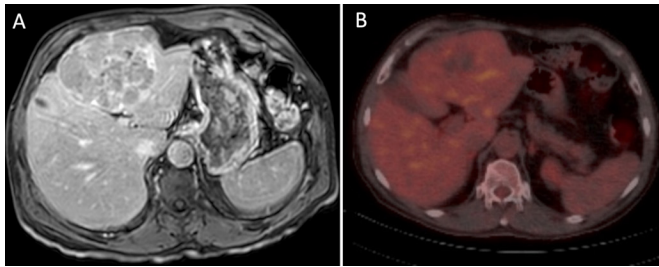


Figure 1 (A) Non-contrast CT and (B) positron emission tomography scan showing a large heterogenous hypodense mass in the liver and central area of photopenia related to necrosis at the junction of segments II and IVa, extending to segments II and III.

connective tissue disease. No clinical symptoms or signs suggestive of rheumatological disorders were found. CIDP, as a paraneoplastic syndrome, became more significant on the differential diagnosis. Haematological studies were performed to rule out haematological malignancies. Serum protein electrophoresis showed non-specific findings, including mild paraproteinaemia (kappa and lambda chains slightly elevated), elevated beta-2-microglobulin and elevated total serum proteins. Urine protein electrophoresis was normal.

A positron emission tomography scan was performed and showed a large heterogenous hypodense mass in the liver with a central area of photopenia related to necrosis, measuring 10×10.9×8.6 cm at the junction of segments II and IVa, extending to segments II and III, suspicious for primary malignancy of the liver (figure 1). No metastatic lesions were detected. Ultrasound imaging showed diffuse hepatic steatosis. For further characterisation of the lesion, MRI of the abdomen was completed and showed a 10.5 cm, slightly exophytic and relatively well-demarcated lesion involving the left hepatic lobe. The features were suggestive of HCC, possibly of fibrolamellar type. A CT-guided liver core biopsy was done to confirm the diagnosis. Pathological examination reported well-differentiated HCC (Hep par-1 positive, glypican positive, CK8/18 (Cytokeratin 8/18) positive, CK7 negative) (figures 2 and 3). Alpha fetoprotein and repeated liver function tests were all normal at that time.

TREATMENT

The patient was started on a course of intravenous immunoglobulin (IVIg) for 5 days. There was a significant improvement in his gait and ability to walk but no tangible improvement in the distal extremity paraesthesia. Within 2 weeks of the initial course of IVIg, his neurological symptoms recurred and became refractory to further IVIg sessions. His motor and sensory symptoms were worsening. Intravenous corticosteroid (Solu-Medrol) was then added to IVIg, leading to an improvement in both upper and lower extremity motor functions. However, such improvement was not enough to allow the patient to walk or to perform daily tasks as he was still dependent on assistance from two persons to move. Medical treatment was then stopped completely.

On reviewing the case at the hospital's tumour board, the decision was taken to intervene surgically given that his paraneoplastic syndrome is refractory to medical intervention. Child-Pugh score was computed prior to surgery and the patient was classified as a 'Class A' candidate. After informed consent was obtained, the patient underwent an uncomplicated laparoscopic

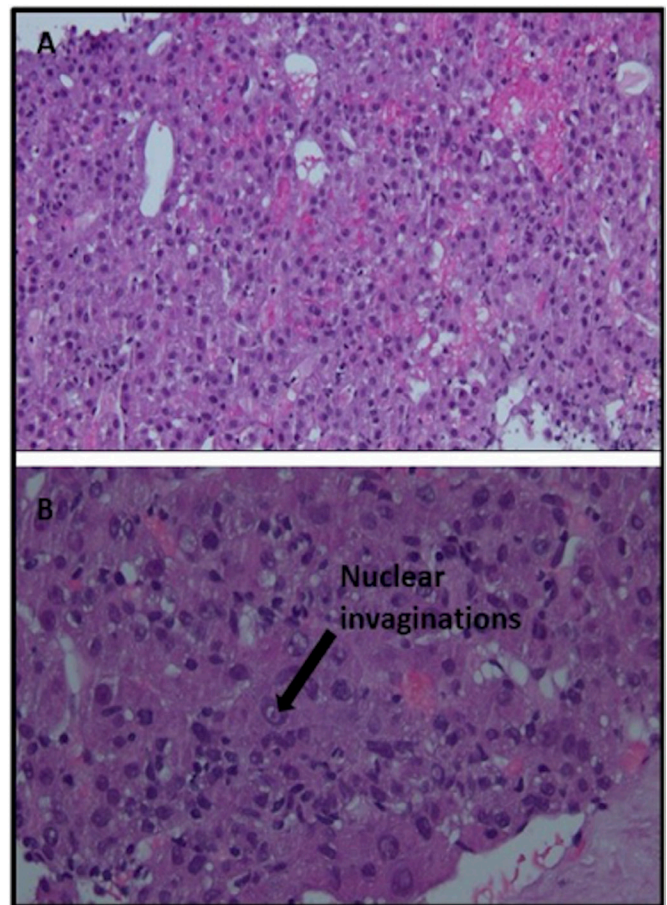


Figure 2 Histology of the liver tumour (H&E stain). (A) Medium-power view, 20×: the tumour cells resemble normal hepatocytes. They have a polygonal cytoplasm. (B) High-power view, 40×: abundant cytoplasm with round to oval vesicular nuclei and nuclear invaginations.

extended left hepatic lobectomy. Staging of the cancer following surgery showed a T1bN0M0 stage tumour.

OUTCOME AND FOLLOW-UP

Following surgery, the patient had an uncomplicated hospital course of 7 days' duration at the end of which he was able to reach objects and to grasp them with his hands. He was also able to walk with assistance from one person. His sensory functions in both upper and lower extremities were also improving prior to discharge. Four weeks later, the patient was examined at a follow-up visit, and neurological assessment showed an exceptional improvement in paresis, numbness in the upper and lower extremity, as well as proprioceptive abnormality following resection of the hepatic tumour. The patient regained most of his motor power and was able to stand up and ambulate with limited support. Two months later, neurological assessment showed a fully functional man who can perform routine tasks of daily activity with minimal effort. One year following the surgery, the patient presented to the clinic to follow up on his condition. Physical examination showed a well-healing surgical scar and his neurological examination was negative. Repeat MRI showed no suspicious lesions in the liver or in the abdomen. The patient's neurophysiological status was well preserved, and he was functionally independent in his daily activities. Consent was taken during this encounter. The patient recently had a virtual

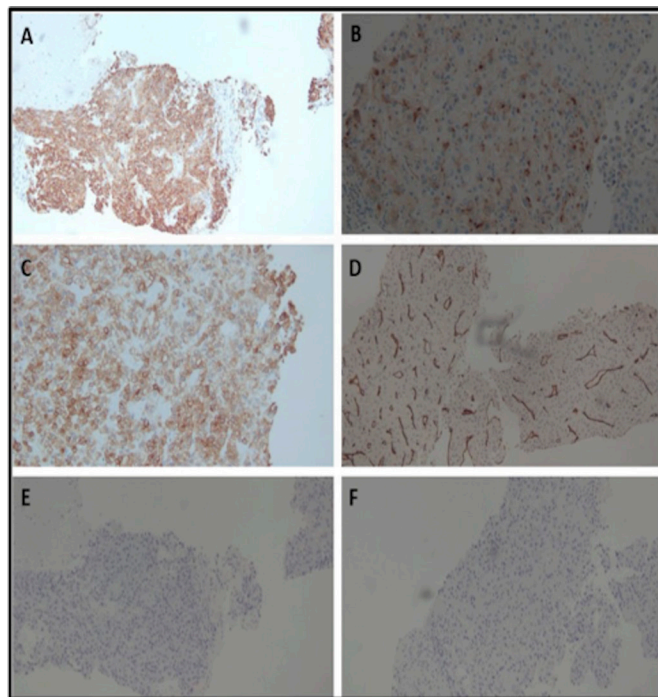


Figure 3 Immunohistochemistry of tumour cells: (A) Hepar-1: positive; (B) glypican: patchy positivity; (C) CK8/18: positive; (D) CD34: highlights tumour vascularity; (E) AFP (Alpha Fetoprotein): negative; and (F) CK7: negative.

checkup appointment, and he reports no change in his neurological status and is fully active.

DISCUSSION

Neurological paraneoplastic syndromes are immune-mediated reactions against the components of the nervous system as a result of molecular mimicry in tumour antigens. Antibodies can be formed against intracellular or extracellular components of the neuronal tissues, leading to neurological manifestations at the level of the central, peripheral or even the autonomic nervous system.^{5,6}

CIDP is a neurological paraneoplastic syndrome that often occurs in the context of haematological malignancies, such as Hodgkin's and non-Hodgkin's lymphomas, chronic myelomonocytic leukaemia, Waldenström's macroglobulinaemia, multiple myeloma and hairy cell leukaemia.^{7,8} CIDP is also described in association with breast cancers, lung cancers, intra-abdominal tumours, melanomas and some gynaecological cancers.⁹

The exact pathophysiological mechanism behind such paraneoplastic syndrome is not well understood. Furthermore, a causal relationship has not yet been established between HCC and CIDP.⁹ Nonetheless, CD8+ T cells were found to play a unique role in the pathophysiology of CIDP. Despite the heterogeneity in the clinical presentation among different CIDP subtypes, most of them involve a nerve injury leading to slowing of peripheral nerve conduction in both proximal and distal nerve segments. Such neuronal insult increases the permeability of the endoneurial blood–nerve barrier to T cells, among many other inflammatory cells and molecules, allowing them to enter and create an inflammatory response.¹⁰ When it comes to the diagnosis of CIDP, multiple diagnostic criteria have been suggested. The European Federation of Neurological Societies/Peripheral Nerve Society criteria appear to be the most specific and selective for CIDP diagnosis.¹¹ According to this guideline, all entities that

mimic CIDP should be ruled out first, including multifocal motor neuropathy, IgM monoclonal gammopathy, lymphomas, amyloidosis and some infectious diseases.¹² Electrodiagnostic studies are essential for the diagnosis of CIDP and would show conduction features suggestive of demyelination (slow conduction velocities, conduction blocks, increased temporal dispersion).^{10,12,13} In our case, extensive rheumatological, haematological and infectious work-ups were done, ruling out all potential mimickers of CIDP. Electromyography and neurography were then performed confirming the diagnosis. Sural nerve biopsy was not needed in our patient as it would only be performed if electrodiagnostic studies fail to show nerve demyelination. The main therapeutic modalities used for treatment of paraneoplastic CIDP include pulses of high-dose corticosteroids, IVIG and plasma exchange therapy. While some of the aforementioned regimens quell the immune response, progression and relapse have been seen in around 50% of cases.¹⁰ Five previous cases were described in the literature regarding the occurrence of CIDP in the context of HCC.^{9,10,14–18} In four of them, the paraneoplastic syndrome preceded the diagnosis of the cancer by months, and symptoms of CIDP resolved in response to medical treatment alone.^{15–18} In the last case, 20 patients with pathologically established HCC were followed up at a certain hospital and one of them developed CIDP.¹⁶ All patients in the reported cases were not candidates for radical surgical resection and were treated with chemotherapy, transcatheter arterial embolisation or radiofrequency ablation. In one of the cases, the cancer was diagnosed at advanced stages and palliative care was initiated.¹⁴ In the present case, CIDP diagnosis was made 1 year following onset of the neurological symptoms, and the diagnosis of HCC was then made 2 months following CIDP diagnosis. Medical intervention alone was not effective in resolving our patient's symptoms; his CIDP was refractory to IVIG treatment alone but was partially responsive to a combinational course of IVIG and Solu-Medrol. Our case is unique in that surgical intervention via left hepatic lobectomy of the tumour yielded full recovery of the patient's motor and sensory functions within weeks of the operation. This finding is important as it suggests a causal relationship between HCC and CIDP.

Learning points

- ▶ Chronic inflammatory demyelinating polyneuropathy (CIDP) usually occurs in association with many types of cancers, especially haematological malignancies, and in our case CIDP was associated with hepatocellular carcinoma (HCC).
- ▶ Our case is unique in that radical resection of the primary tumour resulted in full recovery from CIDP, whereas medical intervention alone yielded partial resolution of motor and sensory functions.
- ▶ An extended diagnostic work-up is needed for HCC in patients with CIDP manifestations, including liver function tests, tumour markers, as well as diagnostic imaging modalities.
- ▶ An extended diagnostic work-up would improve the survival of patients in whom CIDP represents an early paraneoplastic manifestation of an underlying primary hepatic malignancy.
- ▶ CIDP should be considered as a differential diagnosis in patients with HCC presenting with muscular weakness rather than attributing the weakness to the cancer itself, as medical treatment of CIDP can still yield some degree of functional improvement in affected patients.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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