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Case Report

Gastric diffuse large B cell lymphoma presenting as paraneoplastic cerebellar degeneration: Case report and review of literature☆

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Abstract Paraneoplastic cerebellar degeneration (PCD) is a type of paraneoplastic neurological disorder (PND) that is associated with many solid tumors, Hodgkin's lymphoma (HL) and very rarely with non-Hodgkin's lymphoma (NHL). We report a case of PCD associated with gastric diffuse large B-cell lymphoma (DLBCL) in a patient who presented with acute onset of giddiness and double vision and had complete remission of the gastric lesion and marked improvement of cerebellar syndrome with rituximab-based combination chemotherapy. A brief review of the literature is also presented.

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☆ This particular case is unique for its rarity and presentation. To the best of our knowledge, this is the first case report of gastric DLBCL associated with paraneoplastic cerebellar degeneration. We hope that this report would help oncologists recognize and treat such rare cases. Peer review under responsibility of The National Cancer Institute, Cairo University.

Introduction

Paraneoplastic cerebellar degeneration (PCD) and other forms of paraneoplastic neurological disorders (PNDs) have been described in association with many solid tumors (like small-cell lung cancer and adenocarcinoma of the breast and ovary), Hodgkin's lymphoma (HL) and very rarely with non-Hodgkin's lymphoma (NHL) [1]. Symptoms of neurological disturbance may precede those of the underlying malignancy. We report a patient who presented with rapidly progressive pan-cerebellar syndrome with encephalopathy and was subsequently diagnosed to have gastric diffuse large B-cell lymphoma (DLBCL). It is a clinical challenge to diagnose such

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a rare presentation of a neoplastic condition. There are no specific therapies for PCD described [2].

Case history

A 68-year-old male presented with a two month history of progressive unsteadiness while walking, tendency to fall to either side, and slurred speech. He had lost about 5 kg of weight in the last 2 months. This was followed by altered behaviour with fearfulness and talking to self for last four days. Patient had progressive difficulty in walking due to gait ataxia and postural instability and required support for ambulation. There were no other systemic or neurological symptoms during this period. There was no significant past medical history. Examination revealed titubation, upbeat nystagmus, truncal and gait ataxia, bilateral limb ataxia, normal sensory examination, brisk deep tendon reflexes and flexor plantar response. He was noted to have fluctuating sensorium, with multifocal rest and action induced myoclonus of limbs and facial muscles. He developed significant worsening of behavioural disturbances during evaluation in hospital with visual hallucinations, and disturbed sleep.

He was evaluated for subacute onset pan-cerebellar syndrome with encephalopathy; the differential diagnoses considered included paraneoplastic or non-paraneoplastic autoimmune encephalopathy, neurosyphilis, intracranial space occupying lesion, and Creuzfeldt Jakob disease. Investigations for the same were carried out. Routine investigations including haemogram, renal and hepatic function tests, serum electrolytes, serum ammonia (27.8; ref: 11–35 μmol/l) and lactate (12.7; ref: 4.5–20 mg/dl) were normal. Thyroid function tests were normal [T3: 83.8, (ref: 71–178 ng/dl); T4: 8.42, (ref: 4.5–12.5 μg/dl); TSH: 1.17, (ref: 0.4–5.5 μIU/ml)], anti thyroid peroxidase antibody was borderline (35.9; ref: upto 34 IU/ml), and serum sample was negative for human immunodeficiency virus (HIV) antibodies and Venereal Disease Research Laboratory (VDRL) test. Magnetic resonance imaging of the brain including diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) and electroencephalogram (EEG) were unremarkable. Routine analysis of the cerebrospinal fluid (CSF) showed 10 cells (9 lymphocytes, 1 polymorph), normal protein and glucose. Repeated CSF cytospin failed to yield any neoplastic cells. Since the above investigations did not provide a clue to the diagnosis, he was evaluated further for possible paraneoplastic aetiology in view of rapidly progressing symptoms. Stool occult blood was positive, while serological markers for paraneoplastic cerebellar degeneration including anti-Yo, anti-Hu, anti-Tr, anti-Ma and anti-Ri antibodies were all negative. Antibodies for autoimmune encephalopathy like N-methyl D-aspartate (NMDA) and LGI-1 were not tested.

Whole body positron emission tomography (PET)–computed tomography (CT) scan performed using 10 mCi of intravenous fluorodeoxyglucose (FDG) showed a 2.3×1.8 cm metabolically active focal mural thickening of the gastric fundus and two small pulmonary nodules in the left lower lobe and the right middle lobe measuring 4 and 3 mm in diameter, respectively (Fig. 1). Upper gastrointestinal endoscopy showed an elevated lesion with surface ulceration in the gastric fundus (Fig. 2A). Histopathology of the lesion showed gastric mucosa effaced with sheets of large mononuclear lymphoid cells with scant cytoplasm and vesiculated nuclei with prominent nucleoli. The cells were CD20 positive, cytokeratin (CK) negative, and CD3 negative, suggestive of DLBCL of the stomach (Fig. 2B and C).

Colonoscopy and bone marrow aspiration were non-contributory. A diagnosis of gastric DLBCL stage IV (pulmonary metastases) with an International Prognostic Index (IPI) score of 4/5 and PCD and limbic encephalopathy was thus made. He

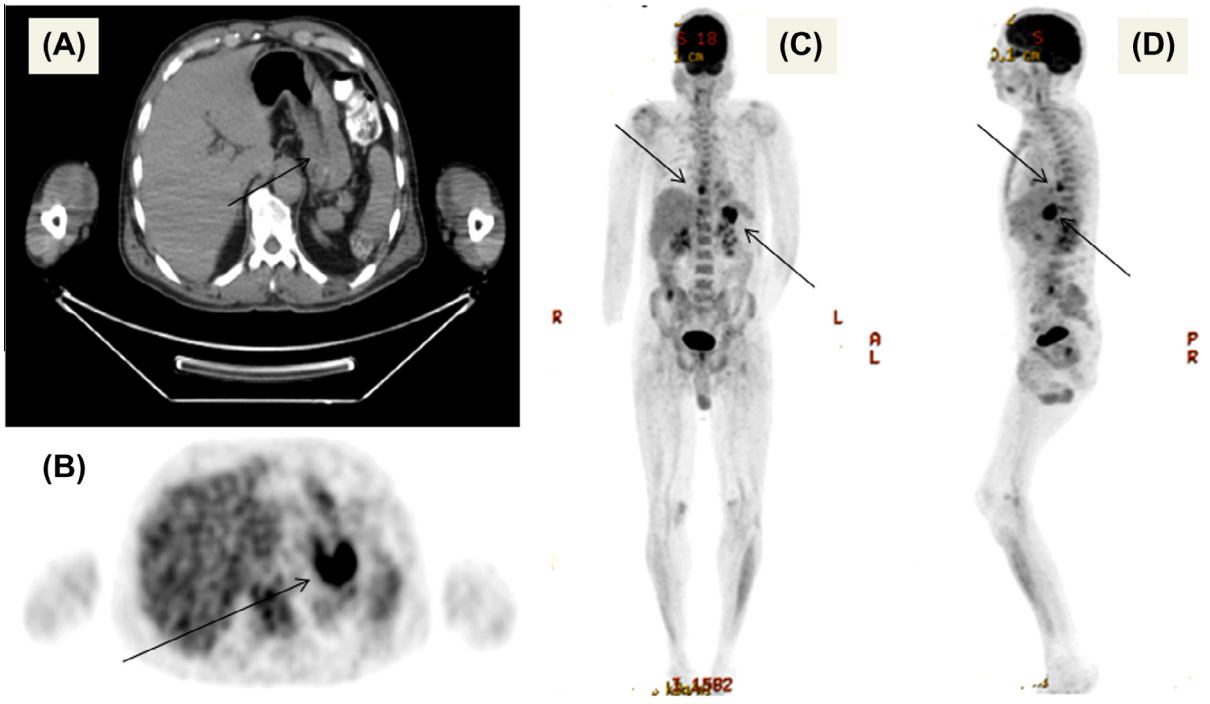

Figure 1 Whole body PET–CT showing stomach wall thickening (A) and areas with increased metabolic activity (B–D).

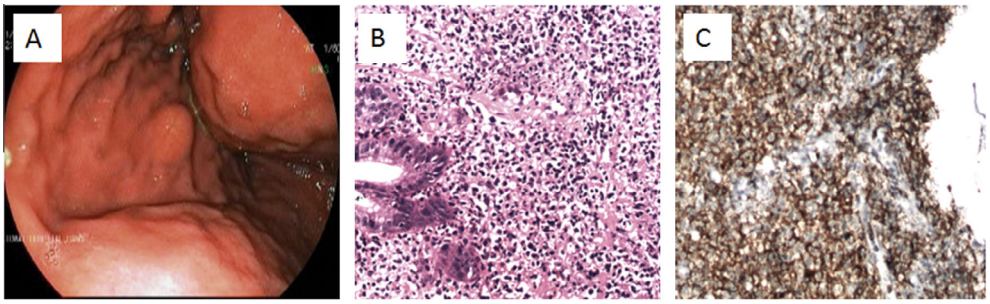

Figure 2 Gastroscopy showing elevated lesion with ulceration (A), Hematoxylin and eosin (H&E) stain of the stomach showing large B cells within the glandular structure (B) and immunochemistry (IHC) showing CD20 positive cells (C).

initially received intravenous methyl prednisolone (1 g daily for 5 days) for PND. There was a significant improvement in encephalopathy (although cerebellar features persisted) and he was referred for management of DLBCL.

He subsequently received combination chemotherapy for gastric DLBCL with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). Interim assessment of the disease status at the end of three cycles showed partial response. Major resolution of neurological symptoms was observed after the 3rd cycle of chemotherapy and maximum improvement was seen two weeks after the completion of 6 cycles of R-CHOP. The patient developed syndrome of inappropriate anti-diuretic hormone secretion (SIADH) after second cycle of R-CHOP which was successfully managed according to institutional protocol. He was also treated with six courses of intrathecal methotrexate, hydrocortisone and cytarabine. At 8 month follow-up, the gastric lesion was in complete remission and there was a significant improvement in cerebellar signs. He is currently on regular follow up.

Discussion

Paraneoplastic syndromes (PS) are remote manifestations of a malignancy not caused by the local effects of compression, infiltration or metastases, but are likely to be due to ectopic production of hormones, antibodies or cytokines [1]. PS has protean manifestations, and may involve the neurological, endocrine, haematological, renal, cutaneous, or other systems, or a combination of these. PND may result in a wide spectrum of disorders of the central nervous system, peripheral nerves, neuromuscular junctions, or muscles (Table 1) [3]. PCD is the most common PND, accounting for about 36% cases [4].

Several salient features in our patient are worth highlighting. Firstly, the association of PS with NHL is quite uncommon (though not unknown) compared to pulmonary, breast and gynaecological tumors. Moreover, the association of PND with gastric DLBCL is rare. In general, the best characterized PND with lymphomas is PCD commonly linked to anti-Tr antibody and rarely to autoantibodies to mouse metabotropic glutamate receptor (mGLuR1). Our patient was negative for auto-antibodies associated with PCD, including anti-Tr.

Secondly, the occurrence of encephalopathy as a paraneoplastic manifestation of lymphoma is not common, as reported in the case series by Briani et al. [5]. However, paraneoplastic limbic encephalitis associated with antibodies to NMDA receptor as well as without an identified autoantibody have been reported in association with HL [6,7].

Table 1 Paraneoplastic neurological disorder (PND) classification by site [2].

1. PND affecting the central nervous system
Subacute cerebellar degeneration
Opsoclonus–myoclonus
Encephalomyelitis
Limbic encephalitis
2. PND affecting the peripheral nervous system
Autonomic neuropathies
Subacute sensory neuronopathy
3. PND affecting the neuromuscular junctions and muscles
Lambert-Eaton syndrome
Dermatomyositis
Myasthenia gravis

Table 2 Auto-antibodies seen in paraneoplastic cerebellar degeneration (PCD) associated with specific cancers [13].

Antibodies	Associated cancer
Anti-Hu	Small-cell lung cancer (SCLC)
Anti-Ri	Breast, gynaecological, SCLC
Anti-Tr	Hodgkin's lymphoma
Anti-yo	Ovarian, breast
Anti-CRMP5/CV2	SCLC, thymoma, gynaecological
Anti-mGluR1	Hodgkin's lymphoma
Anti-VGCC	SCLC
Anti-Ma	Many
Anti-Ta/Ma2	Testis

Finally, our patient presented with rapidly progressive encephalopathy on the background of a pan-cerebellar syndrome, and evaluation for other aetiologies of encephalopathy including structural, metabolic and infectious causes was negative. Antibodies for NMDA and mGLuR1 receptor could not be carried out in this patient. Since his encephalopathy improved with intravenous steroids; it can be indirectly inferred that it was an immune-mediated paraneoplastic manifestation of his gastric malignancy.

In patients with PCD, specific auto-antibodies may be associated with the underlying malignancy (Table 2). The prognosis of PND is variable and the response to immunotherapy is

Table 3 Overview of previously reported cases of PCD with non-Hodgkin's lymphoma.

Age (Yrs)	Cell type (B or T)	Histology	Stage	Lymphoma specific therapy	Response of lymphoma	Response of PCD symptoms	Outcome	Reference
55	Not identified	NA	I	Radiation	CR	Partially improved	Alive	Graus et al. [3]
72	Not identified	NA	II	COP	CR	Stable	Alive	Albert et al. [17]
53	T cell	NHL	IV	COP	PD	Worsened	Dead	Clouston et al. [18]
42	T cell	NHL	III	ACOMPB	CR	Worsened	Dead	Symonds et al. [19]
28	T cell	ALCL	III	CHOP	CR	Worsened	Dead	Ang et al. [20]
47	Composite (HL and NHL)	NA	II	ABVD + rituximab	CR	Partially improved	Alive	Ishihara et al. [21]
68	B cell	DLBCL	NA	NA	CR	Worsened	Dead	Rodis et al. [22]
55	B cell	FL	IV	R-CHOP	CR	Improved	Alive	Shimazu et al. [14]
(Case series $n = 5$) 50–70	All 5 were B-cell lymphomas	Not known	NA	-NA	NA	None improved	2 of 5 died	Briani et al. [5]
68	B cell	DLBCL-stomach	IV	R-CHOP	CR	Improved	Alive	Present case

Abbreviations: ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; ACOMPB: adriamycin, cyclophosphamide, vincristine (oncovin) methotrexate, prednisolone and bleomycin; ALCL: anaplastic large cell lymphoma; CHOP: rituximab, cyclophosphamide, vincristine (oncovin), prednisolone; COP: cyclophosphamide, vincristine (oncovin), prednisolone; CR: complete remission; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; NA: not available; NHL: non-Hodgkin's lymphoma; PCD: paraneoplastic cerebellar degeneration; PD: progressive disease; R-CHOP: rituximab, cyclophosphamide, vincristine (oncovin), prednisolone.

unsatisfactory notwithstanding the fact that these are immune mediated disorders. The type of antibody present in a patient may predict neurological recovery. Auto-antibodies may be directed against intracellular antigens (like anti-Hu, anti CV2, anti-amphiphysin, anti-Ri, anti-Yo, and anti-MA2) or neuronal surface antigens (like voltage-gated potassium channels (VGKC), NMDA receptor, and mGluR1). The former are possibly the result of T-cell mediated immune response and latter are likely due to humoral immune response [8,9]. It has been observed that in general neurological recovery is better with conditions having antibodies against neuronal surface antigens. Additionally, patients with PCD associated with anti-Hu or anti-Yo antibodies are less likely to recover, while those with anti-Tr, anti-Ri, or anti-CV2 antibodies have a better probability of neurologic improvement [10,5,11]. In addition to cancer *per se*, other poor prognostic factors for PCD are old age and other neurological co-morbidities [12].

Autoimmunity in PND targeting intracellular antigens is a T-cell immune mediated response and hence therapy with conventional immunomodulatory agents that target humoral immunity may not affect the pathogenetic mechanisms [8,9]. Rituximab, an important therapeutic agent in the management of B-cell lymphoma, is being increasingly used in the treatment of autoimmune disorders [12,13]. It has been postulated that rituximab leads to a decrease in the number of B cells and consequently reduced secretion of autoantibodies both in serum and CSF, thereby helping in resolution of PND by unknown mechanisms [4].

Briani et al. have reported a series of 29 NHL patients who displayed symptoms of PND, of whom 5 were diagnosed to have PCD. Three out of these 5 patients were positive for auto-antibodies, and none of them had neurological improvement with therapy [5]. Apart from this case series, eight individual cases of NHL have been reported to be associated with PCD [3,14,17–22]. Key features of these reports are summarized in Table 3.

Among the reported NHL cases, the paraneoplastic antibody was identified in only one case of composite lymphoma and it is not clear whether there are specific antibodies for PNS associated with NHL [13]. Treatment with intravenous immunoglobulin (IvIg) has shown benefit when administered within 3 months of onset of symptoms in a series of 15 PCD cases [15]. Some investigators have used triple intrathecal therapy with cytarabine, methotrexate and steroid in addition to IvIg and have reported recovery of PNS [16].

Conclusion

A myriad of PNDs have been described, with and without specific antibodies, and the spectrum is constantly expanding. We have described a rare association of PCD and encephalopathy with gastric DLBCL and reviewed the relevant literature. It is imperative to have a high index of suspicion in order to establish early diagnosis of these rare disorders and therefore institute timely and appropriate treatment.

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