Case Report

High-grade B-cell lymphoma with gastroduodenal involvement showing paraneoplastic cerebellar degeneration: a case report

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Background: Paraneoplastic cerebellar degeneration (PCD), which displays ataxia and other cerebellar symptoms, is the most common paraneoplastic neurological syndrome (PNS). PCD is more likely to occur in individuals with small cell lung cancer (SCLC), gynecological malignancies, and Hodgkin disease, but it is rarely associated with non-Hodgkin lymphoma (NHL).

Case Description: We report a case of PCD accompanying high-grade B-cell lymphoma embedded in an individual's stomach and duodenum, who also presented with acute onset of gait ataxia and slurred speech. The results of the common laboratory tests for neurological disorders, including the paraneoplastic antibody test, were negative. The key to the accurate diagnosis was the positron emission tomography/computed tomography findings. The final diagnosis of high-grade B-cell lymphoma was unclear until the performance of repeated esophagogastroscopy with multipoint deep excavation biopsies. After standard chemotherapy, the patient's gastric tumor was significantly alleviated and cerebellar syndrome was significantly improved.

Conclusions: This case highlights the challenges of diagnosing PNS associated with occult malignancy. PNS patients may present with a variety of neurological disorders; Thus, if any unexplained neurological symptoms appear after a series of specific laboratory and imaging tests, a diagnosis of PNS should be taken into consideration in the differential diagnosis list, as it may help clinicians identify asymptomatic malignancies and ensure patients receive correct treatments in a timely manner. A high-quality endoscopic biopsy is essential, as it helps hematologists make an accurate diagnosis of lymphoma with gastroduodenal involvement based on pathology.

Keywords: Paraneoplastic cerebellar degeneration (PCD); high-grade B-cell lymphoma; esophagogastroduodenoscopy (EGD); stomach and duodenum; case report

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Introduction

Paraneoplastic neurological syndromes (PNSs) represent a group of disorders related to cancers, which do not directly result from the local effects of tumors or metastases, but from related immune reactions (1). Paraneoplastic cerebellar degeneration (PCD) constitutes the most common PNS, which displays ataxia and cerebellar signs. PCD in association with non-Hodgkin lymphoma (NHL) is quite rare. We present a rare case of high-grade B-cell lymphoma with gastroduodenal involvement, presenting as PCD affecting the central nervous system (CNS), which improved dramatically after chemotherapy. We present

Table 1 Laboratory findings on initial evaluation.

Laboratory test	Results [normal range]
Serum	
Hemogram, kidney, and liver function evaluations, and serum electrolytes	Normal
Tumor markers, vitamin B12, folic acid, and LDH	Normal
Coagulation and thyroid function tests	Normal
Tests for HIV, HBV, HCV, and syphilis	Negative
Autoimmune antibody	ANA: negative; Anti-SSA: positive; Anti-SSB: positive
Paraneoplastic antibody evaluation (line blot assay)	Antibodies targeting Yo, Hu, Tr, Ma, Ri, CV2, SOX1, Zic4, GAD65, amphiphysin, PKCγ, recoverin, and titin: negative
Autoimmune encephalopathy antibody evaluation	Antibodies targeting NMDA-R, CASPR2, AMPA1-R, AMPA2-R, LGI1, GABA2-R, and PNMA2: negative
Cerebrospinal fluid	
Leukocyte count, /L	24×10^6/L, with 100% monocytes
Glucose, mg/dL	62.6 [45–80]
Protein, mg/dL	111 [15–45]
IgG, mg/dL	23.7 [0.48–5.86] with oligo-clonal bands (type II)
Antibody for virus	Negative
Smear for bacteria, fungus	Negative
Cytology	Negative for malignancy
Paraneoplastic antibody evaluation (Line blot assay)	Antibodies targeting Yo, Hu, Tr, Ma, Ri, CV2, SOX1, Zic4, GAD65, amphiphysin, PKCγ, Recoverin and titin: negative
Autoimmune encephalopathy antibody evaluation	Antibodies targeting NMDA-R, CASPR2, AMPA1-R, AMPA2-R, LGI1, GABA2-R, PNMA2: negative

LDH, lactic dehydrogenase; ANA, antinuclear antibodies; anti-SSA and anti-SSB are autoantibodies which are often positive in Sjogren syndrome patients; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobin G.

the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1595/rc).

Case presentation

A 40-year-old male patient was admitted to our hospital with no fever on August 4, 2021. He complained of dizziness and dyspepsia over the previous 2 months, which had rapidly progressed to gait ataxia and slurred speech in 1 week. No additional systemic or neurological signs were observed in the same period. The patient had lost approximately 10 kg in weight over the previous month. He experienced nephrotic syndrome 34 years prior, but had completely recovered (the specific treatment was unavailable, and he was not taking any relevant drugs at the time of admission). He had a 1 pack-year of smoking history and no alcohol or drug use history. His mother died of antineutrophil cytoplasmic antibody–related small vasculitis. He had no familial history of any related illnesses. He was an office clerk with no occupational hazards identified but became unable to work due to his neurological symptoms. He denied exposure to sick individuals or tick bites and had no recent travel history.

A neurological examination revealed a series of cerebellar signs, including dysarthria, limb ataxia with a wide-based gait, and positive Romberg sign. The patient's muscle strength, sensation, and deep tendon reflexes were intact in all extremities. He had normal cognitive function, and a systemic evaluation revealed no palpable lymphadenopathy. The patient's laboratory results are set out in *Table 1*. His transcranial doppler results revealed no abnormalities.

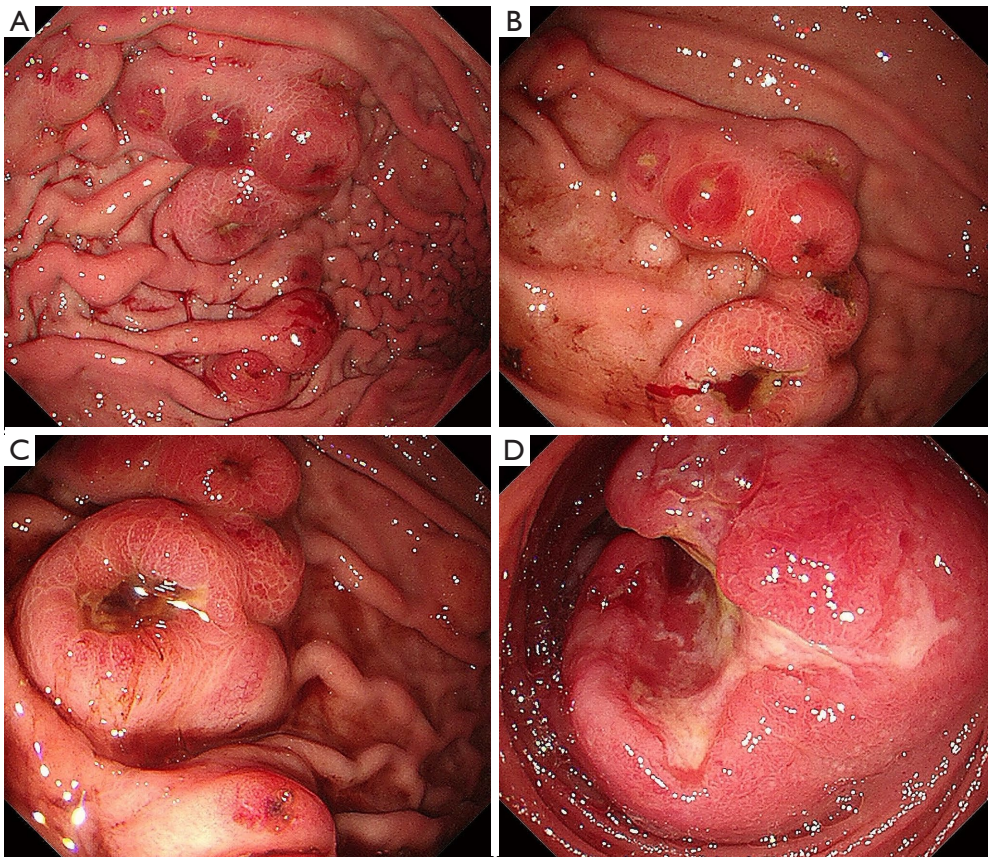

Figure 1 Endoscopic images. (A) Multiple uplifted lesions (with diameters of about 1.0–1.5 cm) were densely distributed in the central part of the greater curvature of the gastric body. (B,C) Some lesions were fused, some were submucosal bulges, and others were craterlike with ulceration on the top. The surrounding mucosa showed apparent congestion and edema. (D) Large irregular masses were observed in the proximal ascending part of the duodenum and were accompanied by deep "dirty" ulceration.

Magnetic resonance imaging of the brain suggested only a few abnormal dotted signals in the white matter of the bilateral frontal lobe with a T1-weighted image (T1WI) equal signal, T2WI/fluid-attenuated inversion recovery (FLAIR) high signal, and diffusion-weighted imaging (DWI) no–abnormal dispersion signal, which could not explain his severe neurological symptoms. Whole-body ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) revealed local gastric wall thickening on the fundus and greater curvature of the stomach with multiple sites of increased radioactive uptake [maximum standardized uptake value (SUVmax) 26.49]. The same appearance was also observed in the ascending part of the duodenum (SUVmax 31.59). The uptake of multiple mesenteric lymph nodes was also slightly increased (SUVmax 2.84). Conversely, the liver, spleen, and superficial lymph nodes showed no increased metabolic uptake. An esophagogastroduodenoscopy (EGD) revealed multiple elevated lesions with surface ulceration in the gastric body. A large, elevated lesion was found at the distal end of the descending part of the duodenum that was almost blocking the lumen. The histopathology of the lesion only showed inflammation; however, PNS was still highly suspected. The patient was treated with intravenous immunoglobulin for 5 days but did not improve before being transferred to our hospital.

A repeated EGD was immediately arranged, which showed multiple uplifted lesions densely distributed in the central part of the greater curvature of the gastric body. Large irregular masses were observed in the proximal ascending part of the duodenum (*Figure 1*). Deep excavation biopsy was performed, and the obtained tissue was hard and bled easily. The pathology slices showed medium to large, atypical lymphocytes infiltrating the lamina propria of the gastric and duodenal mucosa without any intact lymph node

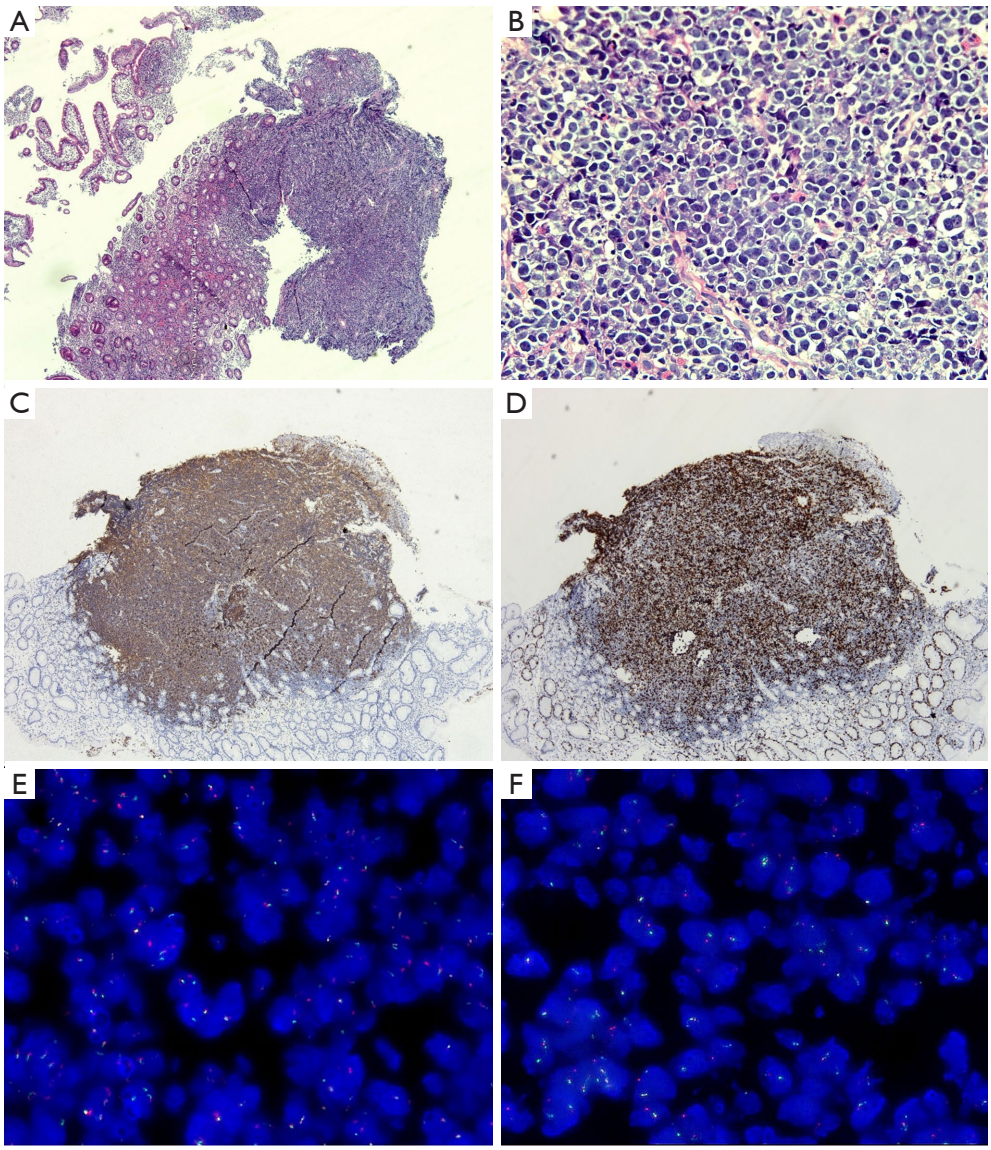

Figure 2 Pathological images. (A) Diffuse lymphoid cells were infiltrated in the lamina propria of the gastric mucosa; the normal structure of lymph nodes had disappeared (40×, HE). (B) Medium to large, atypical lymphocytes infiltrated with round or oval nuclei and 1–2 nucleoli (400×, HE). (C) CD20 was diffuse positive (40×, IHC). (D) The Ki67 proliferation index was about 70–80% (40×, IHC). (E) In MYC, a total of 200 cells were counted. About 20% of the cells in the lesion appeared to have abnormal breaking signals, among which 1 was yellow, 1 was red, and 1 was green [the signal pattern for this probe in normal cells is 2 yellow signals (400×, FISH)]. (F) In BCL-6, a total of 200 cells were counted. About 50% of the cells in the lesion appeared to have abnormal breaking signals, among which 1 was yellow, 1 was red, and 1 was green [the signal pattern of this probe in normal cells is 2 yellow signals (400×, FISH)]. HE, hematoxylin-eosin staining; IHC, immunohistochemical staining; FISH, fluorescence in situ hybridization.

structure. In relation to the cells, the patients results were as follows: all cells were positive for CD20, CD10, Bcl-2, Bcl-6, PAX-5, and CD38; a small amount were positive for CD21, CD3, CD5; 70–80% cells were positive for C-myc and Ki-67; and all cells were negative for MUM1, cyclin D1, CD30, LMO-2, ALK, EMA, CD56, CK, and CD99. These results suggested high-grade B-cell lymphoma. The MYC/BCL6 rearrangement was displayed by fluorescence in situ hybridization (FISH) (*Figure 2*). Bone marrow aspiration and a biopsy showed no infiltration. Thus, a final

diagnosis of PCD secondary to high-grade B-cell lymphoma involving the stomach and duodenum with MYC/BCL6 rearrangement stage IVB and an International Prognostic Index score of 3 was made.

The patient initially underwent THP-COP chemotherapy (cyclophosphamide, pirarubicin, vincristine, and dexamethasone) combined with rituximab and zebutinib, which was followed by intravenous immunoglobulin treatment for 4 days. After the first course of chemotherapy, his neurological symptoms did not improve significantly. Subsequently, he was switched to R-DA-EPOCH (rituximab, etoposide, epirubicin, vindesine cyclophosphamide, and prednisone) chemotherapy for the second course. Surprisingly, an EGD showed only 1 IIa+IIc lesion in the upper part of the greater curvature, with scarlike changes in the center. No evidence of lymphoma was found by pathological examination. No duodenal lesions were found, but this was possibly due to the inadequate assessment of the distal duodenum. His cerebellar ataxia showed gradual improvement with treatment. During chemotherapy, he experienced some side effects, such as constipation, which improved after symptomatic treatment. After the third course of chemotherapy (R-DA-EPOCH with zebutinib), he could sit up in bed alone and even walk with family support for several meters. His dyslexia improved significantly as his speech regained clarity. Repeat PET/CT was carried out after the fourth cycle of chemotherapy (R-DA-EPOCH with zebutinib), which showed no abnormal foci of increased radioactivity in the stomach wall but did show increased focal radioactivity in the ascending duodenum with an area of 0.9 cm × 1.3 cm × 1.5 cm and an SUVmax of 13.6. He was advised to undergo further chemotherapy at the hematology department.

This case report has been approved by the Bioethics Committee of Beijing Friendship Hospital, Capital Medical University (No. 2022-P2-057-01). All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In PNS, neurological symptoms are associated with the tumor but independent of the local effect of the lesion itself or the related metastases. Only approximately 0.3–1% of individuals with tumors experience PNS, which can affect various structures of the nervous system, including the brain, spinal cord, peripheral nerves, neuromuscular junction, and muscles (2). Diverse neuronal proteins expressed by cancer cells trigger immune reactions that inappropriately target the nervous system, resulting in neurological impairment.

Neurological symptoms constitute the initial manifestation of malignant tumors in approximately 70% of PNS cases (3). Most PNS cases develop acutely or sub-acutely. About two-thirds of cases precede tumor development by up to 4 years (2). PCD represents the most common PNS. Prodromal symptoms, including a viral-like illness, dizziness, nausea, and vomiting, are followed acutely to subacutely by gait unsteadiness that quickly progresses to ataxia and diplopia, and frequently nystagmus, dysarthria, and dysphagia. Blurred vision, oscillopsia, transient opsoclonus, and cognitive deficits may also arise (4). In the current case, cerebellar syndrome constituted the initial presentation, and the diagnosis of high-grade B-cell lymphoma was made roughly 6 weeks later.

A definite PNS diagnosis requires a classical syndrome and the identification of a neoplasm within 5 years of PNS onset with or without well-characterized onconeural antibodies (5). A patient with classical PNS should undergo a multisystem evaluation to exclude other diseases.

Multiple PNSs are induced by immune reactions, which frequently manifest as antineuronal antibodies measurable in serum and cerebrospinal fluid (6). The onconeural antibodies typically associated with PCD include Purkinje cytoplasmic antibody 1 (PCA-1, Yo), Purkinje cytoplasmic antibody Tr (PCA-Tr, Tr) and metabotropic glutamate receptor 1 (mGluR1) (7). The presence of antibodies against intracellular onconeural autoantibodies highly suggests an underlying tumor. As only about 60% of the PNSs affecting the CNS have detectable antineuronal antibodies, a negative result does not rule out paraneoplastic disease (2).

In patients with subacute cerebellar degeneration but no typical antibodies or other etiologies, FDG-PET should be carried out if the initial tests cannot identify the underlying malignancy. FDG-PET is widely regarded as the prime imaging method for detecting tumors in cases of paraneoplastic syndromes (8-11). In the current case, PET provided important clues that guided the diagnosis.

PCD is preferentially associated with SCLC, gynecological tumors, and Hodgkin disease (2). PCD is rarely associated with NHL, and Briani *et al.* found NHL

Table 2 Cases of NHL with stomach involvement associated with paraneoplastic cerebellar degeneration

Ref.	Age (years)/Sex	Histology	Treatment	Response of lymphoma	Response of PCD	Outcome
(13)	57/Male	DLBCL	R-CHOP	PR	Stable	Alive
(14)	68/Male	DLBCL	IVMP, R-CHOP	CR	Improved	Alive
Present case	40/Male	High-grade B-cell lymphoma	IVIG, R-THP-COP with zebutinib, R-DA-EPOCH with zebutinib	PR	Improved	Alive

NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; PCD, paraneoplastic cerebellar degeneration; R-CHOP, rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; R-THP-COP, cyclophosphamide, pirarubicin, vincristine and dexamethasone combined with rituximab; R-DA-EPOCH, rituximab, etoposide, epirubicin, vindesine cyclophosphamide, prednisone; PR, partial response; CR, complete response.

in only 5 of 21 PCD cases (12). PCD associated with NHL involved in the stomach is rare; indeed, to date, only 2 individual cases have been reported (13,14). *Table 2* lists the main features of these reports. Interestingly, this patient is the first reported case of double-hit high-grade B-cell lymphoma complicated with PCD with gastroduodenal involvement.

There are 3 major injury patterns for lymphoma with gastric involvement recognizable by endoscopic assessment, including ulceration, diffused infiltration, and polypoid mass (15). The performance of our patient upon EGD was relatively impressive. Standard endoscopic biopsies frequently reveal nothing, and have low diagnostic potential, as they only examine superficial mucosa. In studies examining infiltrative gastric cancers, conventional biopsy indicates positive results in only half of the samples. Sensitivity can be enhanced by using large-valve biopsy forceps (16). The diagnostic potential of large-valve biopsy forceps is markedly increased in combination with various biopsies from a range of sites, including the stomach, gastroesophageal junction, duodenum, and abnormal-appearing areas (17). In the current case, the pathological results of the first biopsy at another hospital were negative, which might have been due to the relatively superficial biopsy depth and lack of biopsy sites. The pathology became positive after an operation with an adequate number of large-valve forceps biopsies.

In the current case, the PNS greatly affected the patient's quality of life, but the malignant tumor had no remarkable symptoms. Primary tumors can be successfully treated in many patients; however, paraneoplastic symptoms frequently persist and impair the quality of life of patients, even more than does the underlying tumor. The present case revealed a rare association between PCD and high-grade B-cell lymphoma with gastroduodenal involvement. This case highlights the importance of diagnosing such rare diseases early and of initiating appropriate treatment before the neurological symptoms become irreversible.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1595/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1595/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This case report has been approved by the Bioethics Committee of Beijing Friendship Hospital, Capital Medical University (No. 2022-P2-057-01). All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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