Case report

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PARANEOPLASTIC NEUROLOGICAL SYNDROME IN A PATIENT WITH HODGKIN LYMPHOMA

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Cancer patients can develop paraneoplastic neuropathy, which cannot be explained by tumors, metastases, infections, or side effects of cancer treatment. We present a case of a 38-year-old patient of male gender with weight loss, night sweats, and weakness. He exhibited sensory loss, paresthesias, and allodynia in both lower extremities. White blood cells were 20 x 10^9/L, and C-reactive protein was 40 mg/L. Viral markers indicated no signs of an active infection. Ultrasonography showed several peripheral lymph nodes with reduced echogenicity. Lung computed tomography detected aggregated lymph nodes in jugular regions and mediastinum. The physical examination revealed swollen lymph nodes in the right supraclavicular region. Brain and spinal magnetic resonance were normal. Cerebrospinal fluid cytology ruled out infectious and malignant involvement. Nerve conduction studies revealed decreased amplitude in the lower extremities, with the inability to elicit sensory and motor responses. Nerve conduction studies revealed decreased amplitude in the lower extremities, with the inability to elicit sensory and motor responses and diminished F response. The patient had symmetrical, ascending neuropathy with absent deep tendon reflexes, indicating sensory-motor polyneuropathy. The biopsy of the lymph node confirmed mixed cellularity Hodgkin lymphoma. The patient started on a chemotherapy regimen including doxorubicin, bleomycin, vinblastine, and dacarbazine. Intravenous immunoglobulins were administered. Partial improvement was noted, with prolonged physical therapy. When neurological symptoms are associated with a tumor or positive onconeural antibodies, paraneoplastic neuropathy can be diagnosed. Timely recognition is crucial since any delay in treatment can be detrimental.

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Key words: *lymphoma, cancer, neuropathy, onconeural antibodies*

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Introduction

Hodgkin lymphoma is a monoclonal lymphoid neoplasm characterized by an excellent prognosis. Neurological symptoms linked to different lymphoma subtypes can appear at any stage of the disease, impacting various parts of the nervous system. In Hodgkin lymphoma, the involvement of the peripheral nervous system is a key aspect.

Neurologic symptoms in Hodgkin lymphoma may arise from nervous system invasion due to chemotherapy and radiotherapy, mass compression, infection, or as paraneoplastic neuropathy (1). Paraneoplastic neuropathies, occurring in cancer patients, lack direct and localized consequences of the underlying tumor and are not attributed to metastasis, opportunistic infections, or adverse events of the treatment (1, 2). The prevalence of paraneoplastic neuropathy in Hodgkin and other lymphomas is less than 1% (3).

Hodgkin lymphoma is linked to distinct paraneoplastic conditions, such as primary central nervous system angiitis, limbic encephalitis, and degeneration of the cerebellum (3). Early detection of the underlying tumor is crucial for improving or stabilizing paraneoplastic neuropathy.

This work aims to present a case study of a patient who developed sensorimotor neuropathy during the early stages of Hodgkin's disease, emphasizing the importance of timely tumor detection.

Case report

We present a case of a 38-year-old patient of male gender, with weight loss, night sweats, and weakness, with complaints that started gradually and asymmetrically, and pains and tingling in the distal parts of the hands. Soon after, severe pain, paresthesias, allodynia, and exhibited sensory loss in the lower extremities begin, in both lower extremities. He complained of asymmetric numbness in the lower limbs, as well as gastrointestinal dysmotility. Detailed examinations were undertaken. The physical examination revealed swollen lymph nodes in the right supraclavicular region. Paraneoplastic etiology was suspected in this patient. In laboratory findings, white blood cells were elevated (20 x 10^9/L), and C-reactive protein 40 mg/L. Viral markers indicated no signs of an active infection. Ultrasonography showed several peripheral lymph nodes with reduced echogenicity. Ultrasonographic observations indicated multiple hypoechoic peripheral lymphadenopathies. Abdomen and lung computed tomography revealed detected aggregated lymph nodes in jugular regions, anterior chest wall, mediastinum, and abdominal para-aortic lymphadenopathy (Figures 1 and 2).

The biopsy of the lymph node confirmed mixed cellularity Hodgkin lymphoma. A neurological examination indicated significant limb weakness, a small reduction in vibratory and joint position sensations, areflexia, and the involvement of pinprick, temperature, and light touch sensations with severe joint position and vibratory

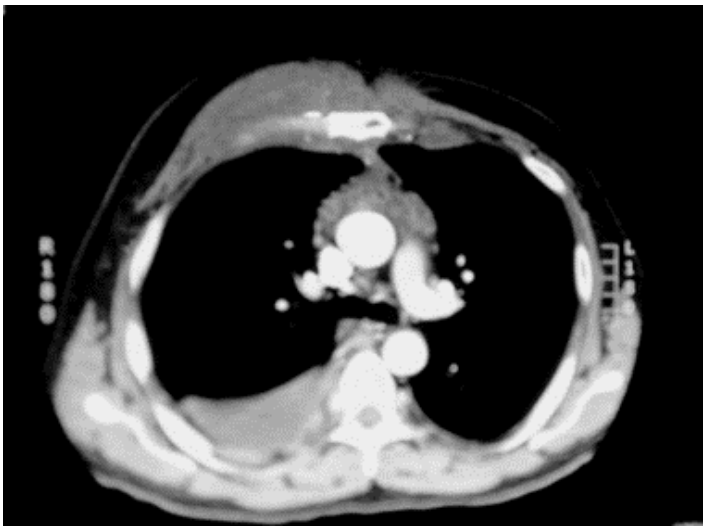

Figure 1. Thoracic computed tomography shows mediastinal lymph nodes, tumor masses in the anterior chest wall, and conglomerated lymph nodes in jugular chains

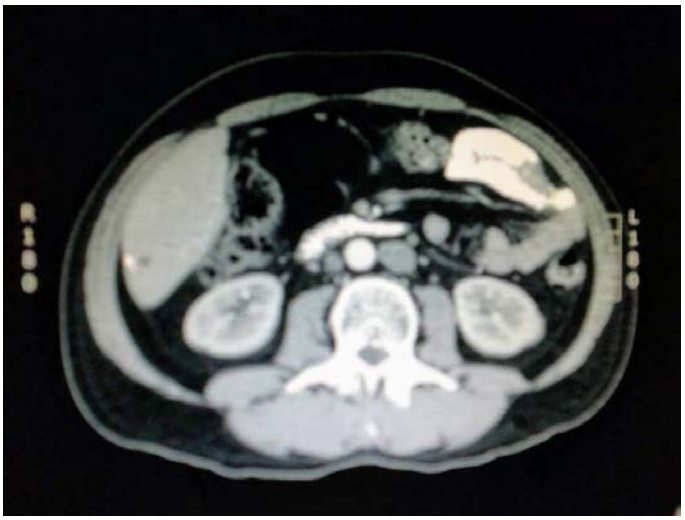

Figure 2. Abdominal computed tomography (para-aortic lymph nodes)

impairment. He exhibited symmetrical ascending neuropathy and deep tendon reflexes were absent. There were no respiratory complaints, and the cranial nerves were normal. Electrical tests revealed reduced distal motor delay and sensory-evoked potentials with standard sensory speed and marginally reduced motor conduction velocities. Nerve conduction investigations in the lower extremities revealed reduced amplitude, with the inability to elicit sensory and motor responses. The F reaction was decreased. The patient had rapidly progressive sensory neuropathy. Cerebrospinal fluid cytology was used to rule out infectious and malignant involvement. Analysis of the cerebrospinal fluid revealed a protein level of 327 mg/dL and no leukocytes. Brain and spinal magnetic were normal. Laboratory tests were positive on serum anti-Hu antibodies, and the other onconeural antibodies were negative. The findings supported sensorimotor neuropathy. Immunomodulatory therapy for neuropathy was administered alongside antineoplastic treatments. Intravenous immunoglobulin was given at a dosage of 400 mg/kg/day for 5 days. A chemotherapy regimen consisting of vinblastine, bleomycin, doxorubicin, and dacarbazine was started. Partial improvement was noted following the initial treatment, and the patient continued with prolonged physical therapy to enhance recovery and support overall function. After being in remission for eight months, the patient suffered paresthesias and gradual weakening over two weeks three weeks after an upper respiratory tract infection occurred. The clinical examination indicated mild to moderate fatigue with just minor sensory impairments. During the monitoring period, identical episodes occurred once more (24 months).

Discussion

Paraneoplastic neuropathies typically manifest before cancer diagnosis or in the early stages, allowing for potential treatment interventions, although they can also develop post-cancer diagnosis (2). These neuropathies may selectively target specific neuron types, leading to pure motor, sensory, or autonomic neuronopathies (4). The majority of cases involve autoimmune mechanisms (1, 2), where an autoimmune reaction develops due to shared antigenic characteristics between the underlying tumor and the nervous system. While antibodies targeting neural antigens have been identified in paraneoplastic neuropathy cases, it is noteworthy that the disorder can occur without the presence of antibodies (5, 6). The complexity of the processes underlying paraneoplastic neuropathies extends beyond the known onconeural and neuronal surface antibodies.

Lymphomas, stemming from abnormal lymphoid cell growth, can give rise to tumors (1). Neurologic manifestations associated with Hodgkin lymphoma are infrequent and are typically observed in advanced stages of the disease (1). Neurologic abnormalities in Hodgkin lymphoma may arise from nervous system invasion due to chemotherapy and radiation, mass compression, infection, or as paraneoplastic neuropathy (7). Considering the underlying immunological disturbance, autoimmune origins are more likely for peripheral neuropathy in Hodgkin lymphoma. In this context, subacute sensory neuronopathy is the type of paraneoplastic neuropathy that occurs most frequently, often presenting with a range of sensory deficits and neuropathic pain (8).

Notably, neurologic neuropathies in the presence of a tumor should not automatically be classified as paraneoplastic syndromes (1). A diagnosis of paraneoplastic neuropathy is established when the disease is associated with a tumor or when onconeural antibodies are detected (1). In our patient, the clinical definition of neuropathy relied on the presence of sensory and motor signs, coupled with reduced or absent deep tendon reflexes without pathological reflexes. The confirmation of neuropathy was obtained through nerve conduction studies. This comprehensive approach aids in understanding and characterizing the intricate relationship between Hodgkin lymphoma and associated neurological complications.

In lymphomas, neuropathies predominantly coincide with monoclonal gammopathy, encompassing conditions like amyloidosis, polyneuropathy organomegaly endocrinopathy monoclonal gammopathy with skin abnormalities, type I cryoglobulinemia, anti-myelin-associated glycoprotein neuropathies, and Waldenström's disease (4, 6). Diagnostic indicators, such as onconeural antibodies (Hu-antibodies, Yo, Ri, Ma, anti-CV2/CRMP5), elevated cerebrospinal fluid protein levels, and the presence of oligoclonal bands in cerebrospinal fluid, aid in discerning the nature of the disease. A thorough investigation into any underlying cancer is imperative (9). A precise definition of paraneoplastic neuropathies is crucial to prevent confusion.

In seronegative sensory neuronopathies, Hu-antibodies, anti-CV2/CRMP5, and anti-amphiphysin antibodies are frequently detected (8). The updated diagnostic criteria for paraneoplastic neurologic syndromes have replaced the term "onconeural antibody" with categorizations based on risk levels: high-risk antibodies (> 70% association with cancer) and intermediate-risk antibodies (30–70% association with cancer) (6). Utilizing a scoring system known as the Paraneoplastic Neurologic Syndromes—Care Score, which incorporates clinical phenotype, the presence of neuronal antibodies, and the presence of cancer, employs a scoring system to classify diagnostic certainty into three levels: possible, probable, and definite paraneoplastic neuropathy (6). Importantly, the presence of cancer is a prerequisite for establishing definite paraneoplastic neuropathy (6). This refined approach enhances diagnostic accuracy and facilitates a comprehensive understanding of the intricate relationship between lymphomas and associated neuropathies.

A diagnosis is established when these neuropathies are associated with malignancies or when oncologic neuronal antibodies are identified. To diagnose definitive paraneoplastic neuropathy in non-classic neuropathies, including sensory and motor neuropathy, the presence of onconeural antibodies should be confirmed, or neuropathy symptoms should show improvement with the treatment of the underlying tumor (2). Detecting onconeural antibodies is challenging in most patients, rendering a diagnosis of unequivocal paraneoplastic neuropathies in lymphomas often impossible (2). Other potential causes of sensorimotor neuropathy comprise infections, autoimmune non-paraneoplastic diseases, malignancies, neurodegenerative disorders, toxins, metabolic issues, alcohol, diabetes, and chronic idiopathic axonal polyneuropathy (6, 8). Chemotherapy-induced peripheral neuropathy stands as a crucial differential diagnosis for paraneoplastic neuropathies after cancer treatment. Emerging challenges in the peripheral nervous system are noted due to various anti-cancer medications, including targeted and immune checkpoint inhibitor therapy (8).

The general therapeutic approach for paraneoplastic neuropathies operates under the assumption that detecting and removing cancer can ameliorate neurological symptoms (8). In our case, the patient underwent intravenous immunoglobulin therapy (2 g/kg in divided doses for 4 to 5 days, repeated monthly) to impede further progression of neuropathy, aligning with current recommendations (10). Determining the precise cause of the regression in neurological findings remains challenging since immunotherapy and treatment of the underlying malignancy were administered concurrently in our patient. Neuropathies that exhibit improvement with tumor therapy are uncommon and occur across various cancers (5). While paraneoplastic neuropathy often manifests before or in the early stages of cancer and may be treatable, studies indicate that it can also develop after cancer diagnosis or in advanced stages (2). Long-term follow-up is imperative (2). In our patient, the identification of paraneoplastic neuropathy coincided with the diagnosis of Hodgkin lymphoma, emphasizing the complexity and importance of managing neurological complications in the context of lymphomas.

Conclusion

The association between paraneoplastic neuropathy and lymphoma is infrequent. The diagnosis of paraneoplastic neuropathy is typically established when the disease is linked to a tumor or when oncologic neuronal antibodies are detected. This case is noteworthy due to the identified correlation between Hodgkin lymphoma and sensorimotor paraneoplastic neuropathy. Timely detection of paraneoplastic neuropathy is paramount, as delays in therapy may occur. A comprehensive clinical examination plays a crucial role in differentiating paraneoplastic sensorimotor neuropathy from other potential causes. This underscores the importance of vigilance in recognizing and addressing neurological complications in the context of lymphomas, contributing to a more nuanced understanding of these complex relationships.

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Prikaz bolesnika

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PARANEOPLASTIČNI SINDROM KOD BOLESNIKA SA HODŽKINOVIM LIMFOMOM

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Paraneoplastična neuropatija javlja se kod osoba sa malignim bolestima i ne može se objasniti prisutnim tumorom, metastazama, infekcijama i neželjenim dejstvom terapije osnovne bolesti. Prikazujemo slučaj bolesnika starog 38 godina koji se javio na pregled zbog gubitka telesne težine, noćnog znojenja, gubitka senzibiliteta u donjim ekstremitetima, bolova, parestezije, alodinije i gubitka čula dodira u donjim ekstremitetima. Laboratorijska analiza krvi pokazala je da je vrednost leukocita bila $20x10^9$/L, a C-reaktivnog proteina 40 mg/L. Markeri virusnih infekcija nisu ukazivali na aktivnu infekciju. Ultrasonografijom je otkrivena višestruka hipoehogena periferna limfadenopatija. Kompjuterizovanom tomografijom pluća otkriveni su konglomerati limfnih nodusa u jugularnim jamama, medijastinumu i prednjem torakalnom zidu. Fizikalnim pregledom utvrđena je bezbolna i umerena limfadenopatija desne supraklavikularne regije. Magnetna rezonanca glave i vrata dala je nalaz koji je bio u granicama normalnih fizioloških vrednosti. Analizom cerebrospinalnog likvora isključeni su infekcija i malignitet. Smanjena amplituda u studijama nervne provodljivosti pronađena je u donjim ekstremitetima, a senzorni i motorni odgovori nisu mogli biti dobijeni. F-odgovor bio je smanjen. Bolesnik je imao simetričnu, uzlaznu neuropatiju i negativne duboke tetivne reflekse. Nalazi su ukazali na senzomotornu distalnu polineuropatiju. Biopsija limfnih žlezda rezultirala je dijagnozom Hodžkinovog limfoma mešovite celularnosti. Započet je polihemoterapijski protokol (doksorubicin, vinblastin i dakarbazin). Neuropatija je lečena intravenskim imunoglobulinima, dozom od 2 g/kg. Zapažen je delimičan oporavak i sprovedena je produžena fizikalna terapija. Kada su neurološke tegobe poput ovih kod prikazanog bolesnika povezane sa malignitetom ili sa pozitivnim onkoneuronskim antitelima, može se postaviti dijagnoza paraneoplastične neuropatije. Važno je blagovremeno prepoznati bolest da bi lečenje bilo uspešno. Rana dijagnoza tumora najbolja je garancija za poboljšanje ili stabilizaciju paraneoplastične neuropatije.

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***Ključne reči**: limfom, malignitet, neuropatija, onkoneuronska antitela*