Case report

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PARANEOPLASTIC NEUROLOGICAL SYNDROME IN A PATIENT WITH HODGKIN'S LYMPHOMA

Jelena Vulović[1], Snežana Knežević[2,3],Marijana Jandrić-Kočić[4,5]

[1]General Hospital, Department for Anesthesiology and Reanimation, Paraćin, Serbia
[2]The Academy of Applied Technical Studies Belgrade, Department of Medical Studies, Belgrade, Serbia
[3]University of Kragujevac, Faculty of Medical Sciences, doctoral studies, Kragujevac, Serbia
[4]Health center, Krupa na Uni, Republic Srpska, Federation of Bosnia and Herzegovina
[5]University of Banja Luka, Faculty of Medicine, doctoral studies, Banja Luka, Federation of Bosnia and Herzegovina

Contact: Snežana Knežević,

110 Jug Bogdanova str., 36000 Kraljevo, Serbia;

E-mail: lesta59@yahoo.com

Abstract

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 male patient, who presented with weight loss, night sweat weakness, sensory loss in the lower extremities, severe pain, paresthesias, allodynia, and sensory loss in the lower extremities. White blood cells were $20x10^9$/L, and C-reactive protein was 40 mg/L. Viral markers showed no active infection. Ultrasonography showed multiple hypoechoic peripheral lymphadenopathies. Lung computed tomography revealed conglomerated lymph nodes in jugular chains, mediastinum, and anterior chest wall. Physical examination showed mild paleness and lymphadenopathy in the right supraclavicular area. Brain and spinal magnetic resonance were normal. Infectious and malignant involvement were excluded with cerebrospinal fluid cytology. Reduced amplitude in nerve conduction studies was found in the lower extremities, and sensory and motor responses could not be obtained. F response was reduced. He had symmetrical, ascending neuropathy and negative deep tendon reflexes. The findings supported sensory-motor polyneuropathy. The lymph node biopsy confirmed mixed cellular Hodgkin lymphoma. Doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy protocol were initiated. Intravenous immunoglobulins 2 g/kg were administered. Partial recovery was observed and prolonged physical therapy was carried out. When neurological complaints like those we described in the presented patient show an association with tumor or positive onconeuronal antibodies, a diagnosis of paraneoplastic neuropathy can be made. Early recognition is important as a delay in treatment. Early tumor diagnosis is the best guarantee to improve or stabilize paraneoplastic neuropathy.

Key words: Lymphoma, cancer, neuropathy, onconeural antibodies.

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PARANEOPLASTIČNI SINDROM KOD PACIJENTA SA HODGKIN LIMFOMOM

Jelena Vulović[1], Snežana Knežević[2,3],Marijana Jandrić Kočić[4,5]

[1]Opšta bolnica, Služba anestezije i reanimacije, Paraćin, Srbija
[2]Akademija tehničkih strukovnih studija Beograd, Katedra za medicinske nauke, Beograd, Srbija
[3]Univerzitet u Kragujevcu, Fakultet medicinskih nauka, student doktorskih studija, Kragujevac, Srbija
[4]Zdravstveni centar, Krupa na Uni, Republika Srpska, Federacija Bosne i Hercegovine
[5]Univerzitet u Banjoj Luci, Medicinski fakultet, student doktorskih studija, Banja Luka, Federacija Bosne i Hercegovine

Kontakt: Snežana Knežević,
Jug Bogdanova 110, 36000 Kraljevo, Srbija;
E-mail: lesta59@yahoo.com

Paraneoplastična neuropatija javlja kod pacijenata obolelih od malignih bolesti i ne može se objasniti prisutnim tumorom, metastazama, infekcijama i neželjenim dejstvom terapije osnovne bolesti. Prikazujemo slučaj muškog pacijenta, starosti 38 godina koji se javio na pregled zbog gubitka telesne težine, noćnog znojenja, gubitka senzibiliteta u donjim ekstremitetima, bolove, parestezije, alodiniju i gubitak čula u donjim ekstremitetima. Leukociti u laboratoriji su bili $20x10^9$/L, a C-reaktivni protein 40 mg/L. Markeri virusnih infekcija nisu ukazivali na aktivnu infekciju. Ultrasonografija je pokazala višestruku hipoehonu perifernu limfadenopatiju. Kompjuterizovana tomografija pluća je ukazala na konglomerate limfnih nodusa u jugularnim jamama, medijastinumu i prednjem torakalnom zidu. Fizikalnim pregledom utvrđena je bezbolna i umerena limfadenopatija desne subklavikularne regije. Magnetna rezonanca glave i kičmenog stuba bili su u fiziološkim. 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 je smanjen. Imao je simetričnu, uzlaznu neuropatiju i negativne duboke tetivne reflekse. Nalazi su podržali senzori-motornu distalnu polineuropatiju. Biopsija limfnih žlezda rezultira dijagnozom Hodgkin limfoma, mešovite celularnosti. Započet je polihemoterapijski protokol (doksorubicin, vinblastin i dakarbazin). Neuropatija je lečena intravenskim imunoglobulinima u dozi 2 g/kg. Uočen je delimičan oporavak i sprovedena je produžena fizikalna terapija. Kada su neurološke tegobe poput opisanih kod prikazanog pacijenta povezane sa malignitetom ili pozitivnim onkoneuronskim antitelima, može se postaviti dijagnoza paraneoplastične neuropatije. Blagovremeno prepoznavanje bolesti je važno radi uspešnog lečenja. Rana dijagnoza tumora je najbolja garancija za poboljšanje ili stabilizaciju paraneoplastične neuropatije.

Ključne reči: Limfom, malignitet, neuropatija, onkoneuralna antitela.

Introduction –

Hodgkin lymphoma is a monoclonal lymphoid neoplasm characterized by an excellent prognosis. Neurological symptoms associated with various lymphoma subtypes can manifest at any stage of the disease, affecting different portions 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 event of the treatment (1,2). The prevalence of paraneoplastic neuropathy in Hodgkin and other lymphomas is less than 1% (3).

Hodgkin lymphoma is associated with specific paraneoplastic diseases, such as primary central nervous system angiitis, limbic encephalitis, and cerebellar degeneration (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

A 38-year-old male patient presented with weight loss, night sweat weakness, complaints that started gradually and asymmetrically, and pains and tingling in the distal parts of the hands. Soon after, severe pain, paresthesias, allodynia, and sensory loss in the lower extremities started. He complained of asymmetric numbness in the lower limbs, as well as gastrointestinal dysmotility. Detailed examinations have begun. Physical examination showed mild paleness and lymphadenopathy in the right supraclavicular area. Paraneoplastic etiology was suspected in this patient. In laboratory findings, white blood cells were elevated ($20x10^9$/L), C-reactive protein 40 mg/L, and viral markers showed no active infection. Ultrasonographic observations indicated multiple hypoechoic peripheral lymphadenopathies. Lung and abdomen computed tomography revealed conglomerated lymph nodes in jugular chains, mediastinum, anterior chest wall, and abdominal para-aortic lymphadenopathy (Figures 1 and 2).

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

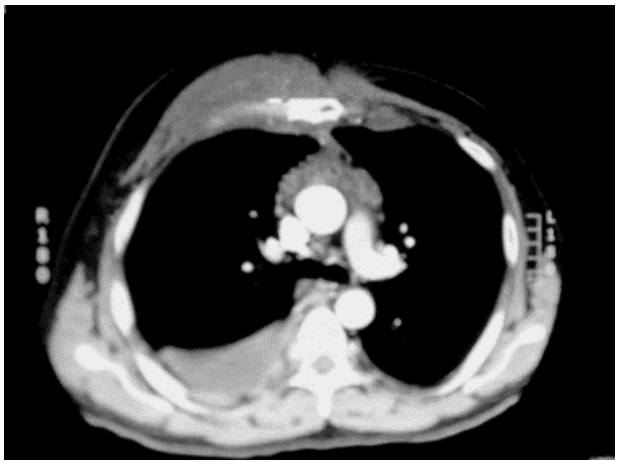
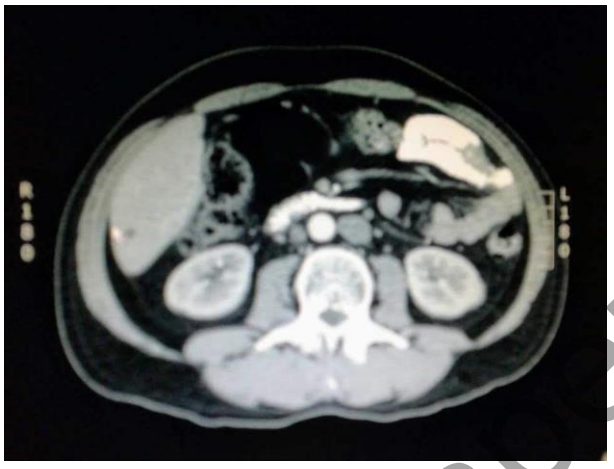


Figure 2. Abdominal computed tomography (para-aortic lymph nodes)



The lymph node biopsy result was mixed cellular 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 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, and sensory and motor responses were not detected. 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 treatment for neuropathy was performed concurrently with antineoplastic therapies. Intravenous immunoglobulin (400 mg/kg/day for 5 days) was administered. Doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy protocol was initiated. Partial recovery was observed and physical therapy continued. 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 result 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. Subacute sensory neuronopathy stands out as the most commonly observed paraneoplastic neuropathy in this context (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. 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). Recent diagnostic criteria for paraneoplastic

neurologic syndromes have replaced the term onconeural antibody with high-risk (>70% associated with cancer) and intermediate-risk (30–70% associated with cancer) antibodies (6). Utilizing a scoring system known as the Paraneoplastic Neurologic Syndromes - Care Score, which considers clinical phenotype, the presence or absence of neuronal antibodies, and the presence or absence of cancer, three levels of diagnostic certainty are proposed: possible, probable, and definite paraneoplastic neuropathy (6). Notably, the presence of cancer is mandatory for defining 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 treatment of the underlying tumor (2). The detection of onconeural antibodies is challenging in the majority of 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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