CASE REPORT
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# Castleman's disease associated with mixed connective tissue disorder and cerebral ischaemia and vasculitis: A rare case and a diagnostic challenge for an infectologist

## Kastlemanova bolest udružena sa mešanim poremećajem vezivnog tkiva i cerebralnom ishemijom i vaskulitisom: redak slučaj i dijagnostički izazov za infektologa

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**Abstract**

**Introduction.** Castleman's disease (CD) or angiofolicullar lymph node hyperplasia is a rare pathologic process characterized by non-neoplastic reactive proliferation of lymphoid tissue. Mimicking clinical and laboratory signs of infection, it could be a great diagnostic problem for an infectologist. **Case report.** We report a case of a 39-year old man who was initially clinically suspected to have an infectious central nervous system (CNS) affection, having most similar appearance to neurotuberculosis. Malignancy with bone metastases and lymphoma were also among many possible diagnoses. The patient was later histologically confirmed to have Castleman's disease, analyzing the enlarged inguinal lymph node, which was the key point in rejecting the suspicion of malignancy and tuberculosis. By further analyses, the patient was diagnosed to have mixed connective tissue disorder (MCTD). Vasculitis of mesencephalon and thalamus was detected by magnetic resonance imaging. **Conclusion.** CD with CNS involvement is very rare as well as CD with MCTD association, making this case even more unique. This case report underlines the importance of definitive histological diagnosis in patients with lymphadenopathia associated with systemic involvement and the need of additional immunological and radiological examinations, as well.

**Key words:**
**castleman disease; diagnostic techniques and procedures; diagnosis, differential; neurologic manifestations; histology.**

**Apstrakt**

**Uvod.** Kastlemanova bolest (KB) ili angiofolikularna hiperplazija limfnih čvorova je redak patohistološki proces koji se karakteriše ne-neoplastičnom reaktivnom proliferacijom limfnog tkiva. S obzirom da imitira kliničke i laboratorijske znake infekcije, može predstavljati značajan dijagnostički problem za infektologa. **Prikaz bolesnika.** Predstavljamo tok bolesti tridesetdevetogodišnjeg muškarca kod koga je u početku bila postavljena klinička sumnja na infekciju centralnog nervnog sistema (CNS), koja je najviše podsećala na neurotuberkulozu. Među ostalim mogućim dijagnozama našli su se i malignitet sa metastazama u kostima i limfom. U daljem toku, kod bolesnika je histološkom analizom limfnog čvora utvrđena KB, što je bilo presudno u odbacivanju sumnje na malignitet i tuberkulozu. Dodatnim analizama je kod bolesnika utvrđena mešovita bolest vezivnog tkiva (MBVT). Magnetnom rezonancom otkriven je vaskulitis mezencefalona i talamusa. **Zaključak.** Kastlemanova bolest sa zahvatanjem CNS-a veoma je retka, kao i KB udružena sa MBVT, što zajedno ovaj slučaj čini još jedinstvenijim. Ovim prikazom slučaja naglašava se važnost definitivne histološke dijagnoze kod bolesnika sa limfadenopatijom i pridruženim sistemskim manifestacijama i potreba za dodatnim imunološkim i radiološkim analizama.

**Ključne reči:**
**kastlemanova bolest; dijagnostičke tehnike i procedure; dijagnoza diferencijalna; neurološke manifestacije; histologija.**

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## Introduction

Castleman's disease (CD) represents angiofolicullar lymph node hyperplasia. It is a rare pathologic process of undetermined etiology. It is characterized by non-neoplastic reactive proliferation of lymphoid tissue [1]. CD is one of many causes of the fever of unknown origin [2]. This disease belongs to the field of research of hematology, oncology, rheumatology and virology because it includes episodic systemic inflammatory symptoms, reactive proliferation of morphologically benign lymphocytes and multiple organ system impairment as a result of excessive interleukin-6 (IL-6) and other proinflammatory cytokines. Regarding viral ethiology, there is a human herpes virus 8 (HHV-8) positive and human immunodeficiency virus (HIV) positive, HHV-8 positive and HIV negative, and HHV-8 negative and HIV negative variant of the disease (idiopathic CD) [3]. Unicentric CD (UCD) implies enlargement of one group of lymph nodes. Multicentric CD (MCD) implies enlargement of two and more groups of lymph nodes and it is associated with systemic symptoms appearance, unlike UCD [4].

The latest diagnostic criteria (2017) [5] for diagnosing HHV-8-negative/idiopathic multicentric CD are established by an international working group of 34 pediatric and adult pathology and clinical experts. The group came up with the following major and minor diagnostic criteria for idiopathic multicentric CD. Major diagnostic criteria (need both present to diagnose) are: histopathologically confirmed CD, and enlarged lymph nodes (> 1 cm in short-axis diameter) in two or more lymph node stations. Minor diagnostic criteria are (need at least two out of eleven criteria and at least one laboratory criterion present): elevated C-reactive protein (CRP) (greater than 10 mg/L) or erythrocyte sedimentation rate (greater than 15 mm/hr); anemia (hemoglobin less than 12.5 g/dL for males, and less than 11.5 g/dL for females); thrombocytopenia (platelet count less than 150 k/μL) or thrombocytosis (platelet count greater than 400 k/μL); hypoalbuminemia (albumin less than 3.5 g/dL); renal dysfunction (estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$) or proteinuria (total protein > 150 mg/100 mL); polyclonal hypergammaglobulinemia (total gamma globulin or immunoglobulin G > 1700 mg/dL); constitutional symptoms: night sweats, fever (> 38 °C), weight loss or fatigue; large spleen and/or liver; fluid accumulation: edema, anasarca, ascites, or pleural effusion; eruptive cherry hemangiomatosis or violaceous papules; lymphocytic interstitial pneumonitis [5].

## Case report

A 39-year-old man presented with a 2-month history of predominantly low grade fever (37.2 °C–37.6 °C), weight loss (approximately 15 kg), incoherent speech, intensive headache with nausea and vomitting. Several days before admission to hospital, he had constant feeling of intense neck pain and his family noticed right eyelid drooping and weakness of his arms and legs with consequent movement difficulty. One day before admisson, he was sleepy and confused, according to his family. After examining in a local hospital, he was sent to the Clinic for Infectious Diseases of the Clinical Center Niš, Serbia, as suspected meningoencephalitis.

The patient's past medical history was significant for a couple of rheumatologist visits due to suspected Reynaud's syndrome owing to periodic feeling of numbness in hand fingers (which occurred one year before current illness and the examining plan was not completed). Concerning family medical history, the patient's father died of myasthenia gravis.

Clinical examination at admission revealed somnolence, disorientation, slurred speech, neck stiffness, positive Brudzinski's neck sign, right eyelid ptosis, bilaterally sligthly reduced breath sound, left pretibial edema, billateral inguinal lymphadenopathy, cachexia, maculopapular rash on trunk and proximal lower extremities. During 7-week hospitalization, the periods of normal body temperature, and slightly raised body temperature up to 38 °C and fever ≤ 39 °C were shifting. The level of consciousness varied between full consciousness and sopor, altogether with the right eyelid ptosis, the degree of which increased and decreased in paralel with neck stifness intensity fluctuation until complete regression. During full consciousness, he has permanently complained of pain in bones. Pretibial edema was present throughout the complete hospital stay. The rash dissapeared after the first hospitalization week.

Routine blood investigations revealed increased white blood cells count (14.9 × $10^9$/L) and platelet count (736 × $10^9$/L ), anemia with red blood cells (RBC) count of 3.25 × $10^{12}$/L, hemoglobin level of 91 g/L, hematocrit of 28%, decreased albumines (25 g/L), increased CRP level (118 mg/L), increased procalcitonin level (0.13 ng/mL), low sodium level (128 mEq/L), increased gamma glutamyl transferase (203 U/L), prolonged prothrombin time (20.6%). Autoantibodies levels were within normal range (anti-Sjogren's syndrome-related antigen A and B, anti-scleroderma 70 kD topoisomerase antigen, antisynthetase antibodies, anti-centromeric B, anti-double stranded DNA, antiphospholipid antibodies), except anti-ribonucleoprotein 70 (anti-RNP 70) which was > 200 U/mL and antinuclear antibodies (ANA) screen (6.7 U/mL, cut-off value for positive result is 1.2 U/mL). Level of β2 microglobulin was increased (4.55 mg/mL), however, myeloma was excluded when serum protein electrophoresis detected no monoclonal band, there was a polyclonal increase in gamma-globulins (20.8%). Interleukine-6 (IL-6) value was 12.23 pg/mL (reference range is < 5 pg/mL).

Two cerebrospinal fluid (CSF) analyses (on admission and eleven days after admission) revealed low sugar (0.2 mmol/L and 2.9 mmol/L, respectively), increased microprotein level (3.36 g/L and 1.43 g/L, respectively), decreased chlorine (116 mmol/L and 106 mmol/L, respectively), 265 RBC and 39 RBC, respectively, 159 polymorphonuclear neutrophils (PMN) cells and 0 PMN cells, respectively 15 lymphocytes and 2 lymphocytes. Blood sugar levels were 5.1 and 5.5 mmol/L, respectively. The CSF was xantochromic both times.

Microbiologic analyses findings of the CSF, on admission and eleven days after admission, (routine CSF bacterial and fungal culture, *Mycobacterium tuberculosis* CSF culture and microscopic exams), as well as of the blood (serology

for borreliosis, HIV, syphilis, brucellosis, leishmaniosis, Cytomegalovirus, Epstein-Barr virus, hepatitis B and C and PCR for HHV8) were negative. Findings of the three urine and three blood analyses for *Mycobacterium tuberculosis* (culture and microscopic exam) were negative, likewise.

Bone marrow biopsy sample and tumor markers analyses results were normal (human chorionic gonadotropin beta, alpha-feto protein, gastrointestinal 19-9 antigen, carcinoembryogenic antigen) except prostate specific antigen (11.43 ng/mL) which was explained as reactive benign prostatic hyperplasia by further analysis (prostatic exam, echosonographic and MSCT findings, prostate biopsy results).

Electromyoneurography (EMNG) of the lower limbs detected distal symmetric sensorimotor polyneuropathy.

Magnetic resonance imaging (MRI) of the brain, showed mesencephalic and thalamic lesions suggestive of ischaemia and vasulitis (Figures 1–3).

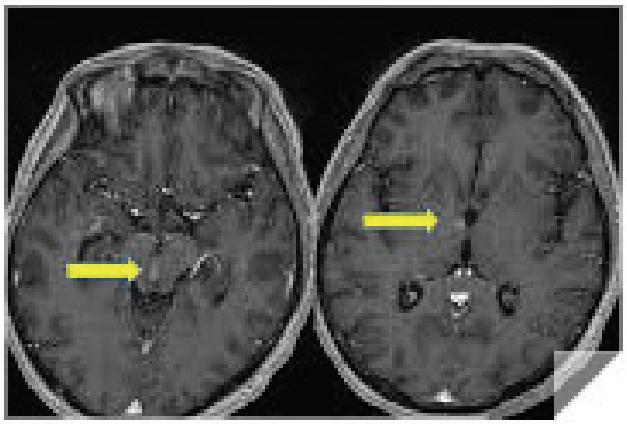

**Fig. 1 – T1 weighted (T1W) axial section presenting areas of altered signals without expansive process, in the right mesencephalic (picture left) and the right thalamic region (picture right), which show post-contrast signal enhancement indicative of vasculitis and consequent cerebrovascular ischemia.**

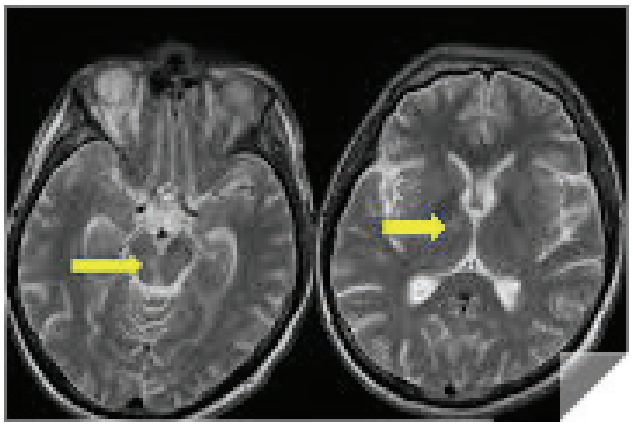

**Fig. 2 – T2 weighted (T2W) axial section presenting areas of altered signals without expansive process, in the right mesencephalic (picture left) and the right thalamic region (picture right), which show post-contrast signal enhancement which is indicative of vasculitis and a consequent cerebrovascular ischemia.**

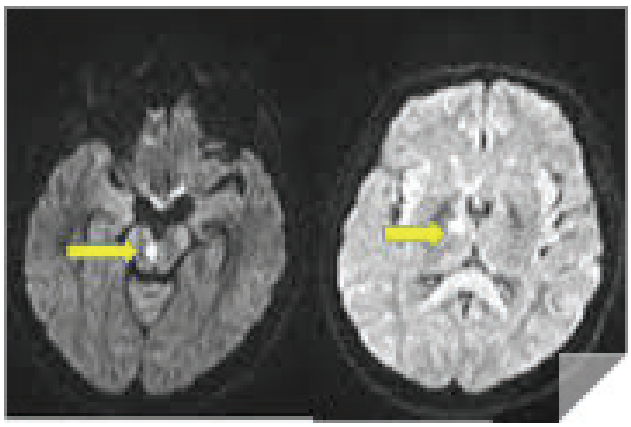

**Fig. 3 – Diffusion-weighted imaging (DWI) sequence showing a restricted diffusion in the right mesencephalic (picture left) and the right thalamic region (picture right) which confirms ischaemic process.**

Multislice computed tomography (MSCT) of chest and abdomen showed lung fibrosis (Figure 4), bilateral pleural effusion, pericardial effusion and mediastinal lymph nodes up to 15 mm; enlarged liver (181 mm in the midclavicular line), and enlarged inhomogenous spleen (maximal height of 140 mm, vertical height of 122 mm). MSCT of the pelvis showed bilaterally enlarged inguinal lymph nodes, both sized 26 mm.

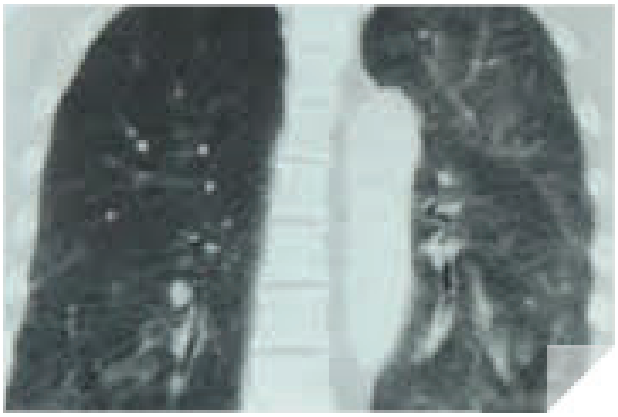

**Fig. 4 – Multislice computed tomography (MSCT) showing an irregulary contoured, 25 × 22 mm and a tape-like, 15 × 8 mm reticular abnormalities of the lungs, in the right middle lobe medial segment, representing pulmonary fibrosis.**

Bone scintigraphy with 99m Technetium marked diphosphono-propanodicarboxylic acid (99mTc – DPD) demonstrated enhanced accumulation of radiopharmaceutical in the mandibular ramus, right sternoclavicular joint, fifth lumbar vertebra, the both femoral necks, left iliac bone, left ischial bone and right knee joint (Figure 5).

Pathohistological analysis of the extirpated inguinal lymph node showed a lymphoproliferative process (angiofolicullar hyperplasia of the lymphoid tissue with hyalinization), suggesting multicentric CD. Bioptic material was analyzed on serial histological sections, colored by hematoxylin-eosin (HE) metod.

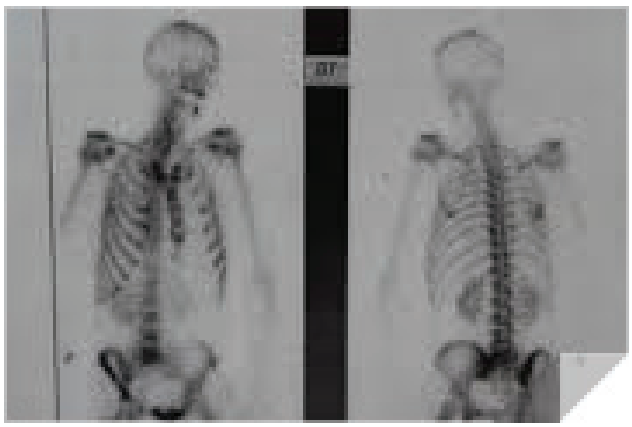

**Fig. 5 – Bone scintigraphy with 99m Technetium marked diphosphono-propanodicarboxylic acid (99mTc – DPD), 3 h after application of 740 MBq osteotropic radiopharmaceutic.**

It contained tissue of the lymph node with globally preserved morphology, with proliferation of the fibrous tissue, which was adequate to its localization (inguinal lymph nodes) and markedly multiplied small blood vessels with slightly expanded and hyalinized walls in places. The finding suggested non-neoplastic lymphoproliferative disorder with regression of germinative centers, abnormal vascular proliferation and hyalinization, and concentric arch-like lymphocytes areas only in places. Prominent interfollicular area contained multiplied non-neoplastic plasma cells, immunoblasts, plasmocytoid monocytes and hystiocytes. Expression of the used immunohistochemical markers did not show neoplastic proliferation. Morphological findings and immunohistochemical analyses corresponded to non-tumorous angiofolicullar hyperplasia of lymphoid tissue that is multicentric CD. Additional application of immunochemistry methods excluded possibility of neoplastic process (the tissue was analyzed for expression of CK AE1/AE3, CD20, CD3, bcl-2, Ki67, CD23 and CD 138 markers) (Figures 6 and 7).

The patient was empirically treated for central nervous system (CNS) infections (parenterally administred – ceftriaxone 2 g/12 h the first day, acyclovir 500 mg/8 h the first day, metronidazole 500 mg/8 h the first day; dexamethason, minimum 8 mg daily, maximum 32 mg daily during first 24 days; mannitol in reducing doses during first 14 days), including *Mycobacterium tuberculosis* brain infection (perorally administred – isoniazid 300 mg daily, rifampin 600 mg daily, pyrazinamide 2,500 mg daily daily, during first 6 weeks; streptomycin 1 g daily during first 10 days and ethambutol 800 mg daily during first 4 weeks) until the proper diagnosis was made.

After hospital discharge and obtaining the correct diagnosis, the patient was referred to a haematologist and started treatment with prednisone, starting with 50 mg daily to 10 mg daily nowdays (in lack of therapy of choice – anti-IL-6 monoclonal antibodies). In first six months after discharge from the hospital the corticosteroid therapy induced only moderate disease remission and symptomatic relief. Twelve months after the discharge, the patient's condition ameliorated significantly in terms of normal body temperature, normal weight, no palpable lymphadenopathy, normal level of consciousness, complete regression of eyelid ptosis, no rash, no edema, achieved walking and speech ability (with the help of the companion due to a slight limb instability) and laboratory markers of inflammation within reference range.

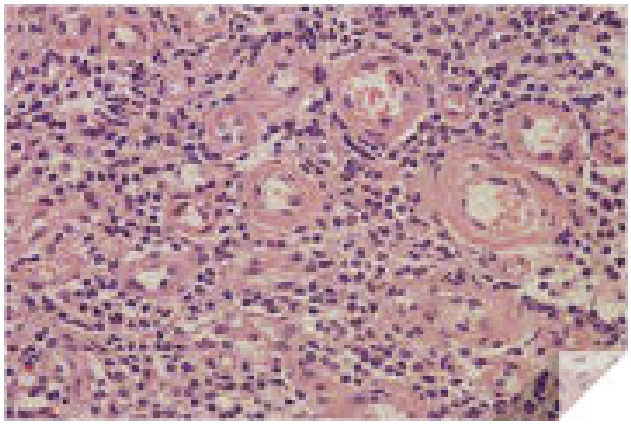

**Fig. 6 – Vascular proliferation and hyalinization of the lymph node (hematoxylin & eosin stain, magnification ×40).**

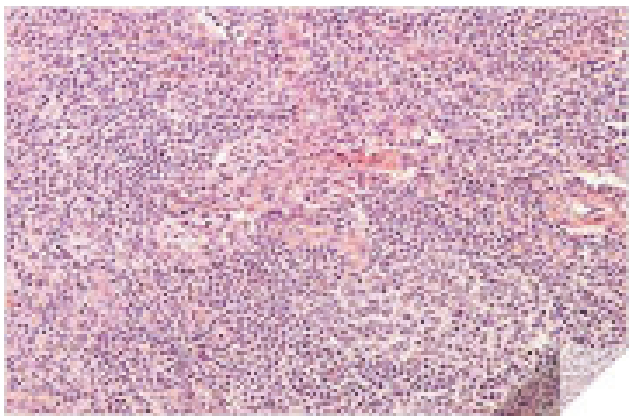

**Fig. 7 – Germinal center regression with hyalinization of the lymph node (hematoxylin & eosin stain, magnification ×20).**

## Discussion

Castleman disease is a very rare disease. Unicentric CD (UCD) is the most common at 16 *per* million person years and occurs at every age. Idiopathic MCD is a less frequent disease with an estimated incidence of 5 *per* million person years [6]. The estimated US 10-year prevalence of MCD was 2·4 per million which is information obtained from data analyses of 59 MCD patients identified between 2000 and 2009 at two the United States MCD referral centres [7]. Until now, there was no presentation of MCD (which is even more rare than UCD) from the Serbian authors, there was only one presentation of an UCD case, published in 2011 [8].

Our patient's findings could be consequent to a number of diseases, including bacterial meningitis, tuberculosis with tuberculous meningitis, cerebritis, cancer with bone and brain metastases, lymphoma, myeloma, systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD)

and other systemic autoimmune disorders. Fever and meningeal syndrome were the reason for admission to the Clinic for Infectious Diseases.

The diagnosis of CD was obtained after the histopathological and immunohistochemical analysis. This was probably the consequence of IL-6 overproduction which induced anaemia, increase of immunoglobulins, increase in inflammatory activity parameters and the formation of autoantibodies, explaining the positive antinuclear antibodies (ANA) test along with physical findings and symptoms [9].

Having in mind our patients bone scintigraphy findings, it was very hard to differentiate them from disseminated bone metastases. However**,** there were some case reports of CD which mimicked MCTD [10]. Further more, SLE is often linked with anti ribonucleoprotein (RNP) positivity and osteopenia [11], and 32% of the patients with multicentric CD have criteria for POEMS syndrome (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) [12]. Our patient fulfills the criteria for multicentric CD associated with the osteosclerotic variant of POEMS syndrome.

Most patients, as our patient, with the generalized form present with systemic symptoms such as fever, weight loss, anemia and hyperglobulinemia. The systemic involvement and histological presentation were the elements for the diagnosis of the multicentric CD. A review of the presence of autoimmune diseases concomitant to CD revealed an association with rheumatoid arthritis, myasthenia gravis, SLE/polymyositis overlap syndrome, MCTD and SLE. The fact that the patients father died due to suspected myasthenia gravis is another brick that straightens the wall of the CD diagnosis [9].

Castleman's disease may occur at any site with lymph nodes and extranodal areas. Castleman's disease is rarely diagnosed in the CNS, with only 13 cases in the literature until year 2005. The origin of intracerebral CD was explained by dendritic cells' participation in immune disregulation in MCD [13, 14].

Cerebral ischaemia, vasculitis and CSF alteration in our patient were most likely the result of POEMS syndrome, presenting as aseptic meningitis [15].

A range of systemic therapies have been utilized in MCD, including cytotoxic chemotherapy agents and antibodies directed against CD20 as well as IL-6 and its receptor (rituximab and siltuximab). Corticosteroids may offer effective symptom relief but, as the duration of response is typically limited, their main role is in combination with chemotherapy or other MCD treatments [16]. We suppose that initial dexamethasone treatment (administred as therapy against intracranial swelling) gave improvement of the patient's immunologically induced symptoms, incidentally targeting IL-6 pathways as a corticosteroid, but not as successful as targeted anti IL-6 therapy would have done it).

Siltuximab has a greater proportion of complete responses and longer progression-free survival for iMCD than rituximab [17]. Our patient fullfied the criteria for iMCD, so the right therapy of choice should have been siltuximab. Castleman's disease can transform into variety of malignancies, particularly non-Hodgkin's lymphoma, and Hodgkin's disease especially if targeted anti-IL-6 antibody therapy has not been implemented [18].

## Conclusion

This case brings together two very rare presentations associated with CD – the MCTD presentation and the cerebral affection, making it even more unique. The whole clinical picture and the laboratory findings make this particular case, as well as any case of CD, a diagnostic challenge for various medical fields specialists.

## REFERENCES


1. *Castleman B, Iverson L, Menendez VP.* Localized mediastinal lymph-node hyperplasia resembling thymoma. Cancer 1956; 9(4): 822–30.
2. *Roca B, Torres V.* Castleman's disease presenting as fever of unknown origine: diagnostic value of fluorodeoxyglucose-positron emission tomography/computed tomography. Am J Med Sci 2009; 337(4): 295–6.
3. *Fajgenbaum DC, van Rhee F, Nabel CS.* HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis and therapy. Blood 2014; 123(19): 2924–33.
4. *JK, Kim Y.* Surgical Management of Unicentric Castleman's disease in the abdomen. Ann Coloproctol 2014; 30(2): 97-100.
5. *Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G,* et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017; 129(12): 1646–57.
6. *Simpson D.* Epidemiology of Castleman disease. Hematol Oncol Clin North Am 2018; 32(1): 1–10.
7. *Robinson D Jr, Reynolds M, Casper C, Dispenzieri A, Vermeulen J, Payne K,* et al. Clinical epidemiology and treatment patterns of patients with multicentric Castleman disease: results from two US treatment centres. Br J Haematol 2014; 165(1): 39–48.
8. *Maric N, Stanic V, Cvijanovic V, Ristanovic A, Kovacevic S, Krivokapic Z,* et al. Surgical treatment of unicentric plasma cell histological type Castleman's disease. Vojnosanit Pregl 2011; 68(9): 795–9.
9. *Muskardin TW, Peterson BA, Molitor JA.* Castleman disease and associated autoimmune disease. Curr Opin Rheumatol 2012; 24(1): 76–83.
10. *Hosaka S, Kondo H.* Three cases of Castleman's disease mimicking the features of collagen disease. Ryumachi 1994; 34(1): 42–7.
11. *Lokesh S, Tony K, Raghupathy VS, Malepati B.* A Rare Case of Mixed Connective Tissue Disease (MCTD) with Intricate Features of Lupus, Polymyositis and Rheumatoid Arthritis Presenting with Severe Myositis. J Clin Diagn Res 2015; 9(3): OD05–7.
12. *Dispenzieri A, Armitage JO, Loe MJ, Geyer SM, Allred J, Camoriano JK,* et al. The clinical spectruma of Castleman's disease. Am J Hematol 2012; 87(11): 997–1102.
13. *Cummings TJ, Gong JZ, Friedman AH, McLendon RE.* Castlemans Disease Confined to the Leptomeninges. Ann Clin Lab Sci 2000; 30(3): 278–82.
14. *Matsumura K, Nakasu S, Tanaka T, Nioka H, Matsuda M.* Intracranial localized Castleman's disease – case report. Neurol Med Chir (Tokyo) 2005; 45(1): 59–65.

15. *Yu H, Yao F, Li Y, Li J, Cui QC.* Castleman disease variant of POEMS syndrome complicated with multiple cerebral infarction: a rare case report and review of literature. Int J Clin Exp Pathol 2015; 8(10): 13578–83.
16. *Chan KL, Lade S, Prince HM, Harrison SJ.* Update and new approaches in the treatment of Castleman disease. J Blood Med 2016; 7: 145–58.
17. *Yu L, Tu M, Cortes J, Xu-Monette ZY, Miranda RN, Zhang J,* et al. Clinical and pathological characteristics of HIV- and HHV-8-negative Castleman disease. Blood 2017; 129(12): 1658–68.
18. *Mohtaram A, Afif M, Sghiri T, Rami A, Latib R, Kettani F,* et al. Coexistence of Hodgkin's Lymphoma and Castleman's Disease: A Case Report with Successful Response to Chemotherapy and Radiotherapy. Case Rep Oncol Med 2013; 2013: 487205.

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