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GAMMA HEAVY-CHAIN DISEASE PRESENTING WITH HYPERCALCAEMIA AND ASCITES

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ABSTRACT

Gamma heavy-chain disease (gHCD) is a rare lymphoproliferative disorder characterised by the production of truncated gamma heavy chains that are not associated with light chains. We present the case of a 79-year-old man with a known history of chronic lymphocytic leukaemia who presented with acute confusion, hypercalcaemia and ascites. Workup revealed monoclonal gamma heavy chains in serum without corresponding light chains. Treatment with a combination of rituximab, bortezomib and prednisone resulted in complete remission, sustained over two years. This case highlights the diagnostic and therapeutic challenges of gHCD and underscores the importance of individualised management.

KEYWORDS

Gamma heavy-chain disease, lymphoproliferative disorder, hypercalcaemia, ascites, rituximab

LEARNING POINTS

- Consider gamma heavy-chain disease in patients with unexplained monoclonal gammopathy and atypical presentations, such as hypercalcaemia and ascites.
- A combination of rituximab and chemotherapy shows an anti-tumour effect in gamma heavy-chain disease expressing CD20.

INTRODUCTION/BACKGROUND

Gamma heavy-chain disease (gHCD) is a rare lymphoproliferative disorder involving lymphocytes, plasmacytoid lymphocytes and plasma cells. It is characterised by the production of a truncated immunoglobulin G (IgG) heavy chain that cannot pair with light chains[1]. With fewer than 200 documented cases, gHCD remains poorly understood. Treatment varies widely, from active surveillance in indolent cases to aggressive multi-agent chemotherapy in symptomatic patients. Due to its rarity and heterogeneous presentation, clinical recognition and management of gHCD remain challenging. We report a case of gHCD in an elderly patient presenting with hypercalcaemia and ascites, successfully treated with a rituximab-bortezomib-prednisone regimen.

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CASE DESCRIPTION

A 79-year-old man with a known history of chronic lymphocytic leukaemia (CLL), Binet stage A, ascites secondary to cirrhosis from congestive heart failure and renal failure, was admitted for acute confusion and a general decline in condition. Over the prior year, the patient had undergone multiple paracenteses, and a haematologic malignancy was suspected. Blood flow cytometry suggested CLL with a Matutes score of 1, showing CD5 and CD10 negativity. Analyses of ascitic fluid, gastric biopsies, a positron emission tomography (PET) scan and serum protein electrophoresis had all returned negative results. In 2023, he presented again with confusion and general deterioration. He was afebrile and disoriented. Blood tests revealed hypercalcaemia (130 mg/l). Hepatic encephalopathy was suspected and treated empirically, but symptoms persisted. Repeat flow cytometry confirmed CLL. Serum electrophoresis identified a monoclonal protein (4 g/dl), and immunofixation revealed monoclonal gamma heavy chains without light chains. Bone marrow biopsy confirmed a B-cell lymphoproliferative disorder with plasmacytic differentiation. Autoimmune markers were negative, and a PET scan showed no hypermetabolic lymphadenopathy. A diagnosis of gamma heavy-chain disease was made. The patient began treatment with rituximab (375 mg/m^2 on days 1, 8, 15 and 22) and prednisone (1 mg/kg on specific days), achieving normalisation of calcium levels and a 15% reduction in monoclonal protein after three doses. Subsequently, bortezomib was added (days 1, 8 and 15 monthly for seven cycles), leading to complete remission. Two years post-treatment, he remains in remission.

DISCUSSION

Heavy-chain disorders are rare B-cell proliferative conditions, including alpha, mu and gamma heavy-chain disease, heavy chain deposition disease (HCDD) and heavy chain amyloidosis. These conditions are marked by monoclonal heavy chains in the serum or urine, without corresponding light chains, often representing an underlying lymphoplasmacytic disorder. Gamma heavy chain disease (gHCD) is the most common of these rare disorders and presents with diverse clinical manifestations, ranging from asymptomatic cases to aggressive lymphoproliferative diseases. Diagnosis relies on detecting an isolated monoclonal γ-heavy chain by serum immunofixation, typically without κ or λ light chains. Histologically, gHCD often shows pleomorphic lymphoplasmacytic infiltrates and may be associated with autoimmune disorders.

Our case contributes to the growing evidence supporting the efficacy of rituximab-based therapies in gHCD, especially in patients with CD20 expression and comorbid autoimmune features. Compared with other reports in the literature, our patient's sustained remission with a combination of rituximab, bortezomib and prednisone supports this approach as a viable treatment strategy in clinically unstable patients.

Three recent studies have reported a wide range of treatment strategies and clinical outcomes in gHCD. In the study by Singer et al., five patients with gHCD or HCDD were treated with various regimens such as CyBorD, BR, V-EPOCH or autologous hematopoietic stem cell transplant[2]. While some patients achieved complete remission, others experienced disease progression, relapse or complications such as sepsis or end-stage renal disease. In the study by Chang et al.[3] six patients, with or without associated lymphoid neoplasms, were managed with either active treatment or a watch-and-wait approach. Asymptomatic patients remained stable, whereas others progressed to aggressive lymphomas. Bieliauskas et al. reviewed 13 gHCD cases[4], with six patients having documented clinical follow-up. Treatments included rituximab, bortezomib/dexamethasone, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), and chlorambucil, with variable outcomes ranging from long-term stability to death from treatment complications.

These findings underscore the considerable clinical and therapeutic heterogeneity of gHCD and the lack of a standardised treatment protocol. They emphasise the importance of individualised therapy, guided by clinical severity, comorbid conditions and immunophenotypic features such as CD20 expression[5].

CONCLUSION

This case illustrates the importance of considering gHCD in patients with unexplained monoclonal gammopathy and atypical presentations, such as hypercalcaemia and ascites. Rituximab-based therapy led to a sustained complete remission in our frail elderly patient, underscoring the potential effectiveness of individualised treatment strategies. Due to the heterogeneous nature of gHCD and lack of standard treatment protocols, further research and case accumulation are essential to establish clearer guidelines for management.

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