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CASE REPORT

Hodgkin lymphoma mimicking the IgG4-related disease: A diagnostic pitfall

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Abstract

This is a diagnostically challenging case that concerns a 29-year-old man with an eight-year history of right-sided neck swelling. The magnetic resonance imaging (MRI) of the neck revealed multiple well-encapsulated, lobulated, matted right cervical lymphadenopathy. He reported significant weight loss, but denied shortness of breath, altered bowel habits, or bone pain. His initial investigations revealed a normocytic hypochromic anaemia, mild leukocytosis, and thrombocytosis. The initial histological findings showed many IgG4-positive plasma cells, but lacked stromal fibrosis, granuloma, obliterative phlebitis, or malignant cells. In addition, the IgG4+/IgG plasma cell ratio was only about 20%. The serum IgG4 subclass was raised at 258 mg/dl, along with a raised serum IgG1 subclass at 3630 mg/dl. His bone marrow aspirate findings showed reactive plasmacytosis without marrow infiltration or acute leukaemia. Multiple myeloma was excluded by the absence of paraproteins in the serum and urine electrophoresis. A working diagnosis of probable IgG4-RD was made, and he was treated with glucocorticoids and azathioprine. However, the neck mass did not resolve, and the serum globulin was persistently high, ranging from 75 g/l to 95 g/l. A repeat biopsy of the neck swelling demonstrated Hodgkin lymphoma (HL) with mixed cellularity, and the Epstein-Barr virus (EBV) RNA-in-situ hybridisation was negative. He was started on chemotherapy and achieved complete remission, with an episode of relapse 9 months later. Salvage chemotherapy was initiated and is currently awaiting haematopoietic stem cell transplantation. This case highlights the need for repeated histopathological evaluation and reflects the complexity and overlap between HL and IgG4-RD.

Keywords: Hodgkin lymphoma, IgG4-related disease, lymphadenopathy

INTRODUCTION

Hodgkin lymphoma (HL) is a less common malignancy of the B-cell lineage, with a bimodal distribution affecting young adults and those above 50. The proposed risk factors for developing HL include viral infection, familial factors, and a state of immunosuppression. Epstein-Barr virus (EBV) has been implicated in the aetiology of HL, and there is an increased risk of developing HL among the immunosuppressed, such as in HIV positive patients.[1] The average age-adjusted incidence of HL in individuals of European ancestry is 2-3 per 100,000 population.[2] The incidence in Malaysian males with age-standardized rates (ASR) was 1.2, 0.9, and 0.7 per 100,000 among the Indians, Malays, and Chinese, respectively. The ASR in Malaysian women was 0.7, 0.6, and 0.4 per 100,000 among the Indians, Malays, and Chinese, respectively.[3]

HL is generally classified into two main subtypes: classical HL (cHL), which accounts for approximately 90% of cases, and nodular lymphocyte-predominant HL (NLPHL), which is observed in about 10% of cases. The cHL

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can further be subtyped into nodular sclerosis HL (NSHL), mixed cellularity HL (MCHL), lymphocyte-rich HL (LRHL), and lymphocyte-depleted HL (LDHL).[2] EBV infection is commonly associated with cHL, particularly MCHL.[4] A biopsy is the definitive procedure for the diagnosis of HL. The cHL typically shows mononuclear Hodgkin cells and multinucleated Reed-Sternberg (RS) cells within an inflammatory background. On the other hand, the NLPHL are malignant B cells with nodular proliferation of lymphocyte predominant (LP) cells surrounded by small B cells and occasionally histiocytes. The RS cells are usually CD30 and CD15 positive, whereas the LP cells are typically positive for CD20.[5]

The treatment of HL depends mainly on the histologic findings and staging. The Cotswolds modified Ann Arbor staging is the most widely used classification system.[6] Curative treatment is the goal of management, in which the main treatment modalities are systemic chemotherapy and radiotherapy. The treatment strategy is based on the stages, patients' age, and comorbidities. Positron Emission Tomography (PET) guided treatment is now the standard treatment in HL, which uses fluorodeoxyglucose (FDG-PET) scans to guide the treatment intensity based on the patient's treatment response to the initial chemotherapy cycle. It allows clinicians to individualise and personalise the treatment strategy to improve the treatment outcome and reduce the treatment toxicity.[7]

IgG4-related disease (IgG4-RD) is a chronic, systemic, immune-mediated fibroinflammatory disorder that affects multiple organs, often mimicking malignancy or autoimmune disorders. The disease can also affect various organs simultaneously, and certain conditions previously considered as unique clinical entities are now considered to be part of IgG4-RD, such as autoimmune pancreatitis, sclerosing cholangitis, Mikulicz's disease, Kuttner's tumour, and orbital pseudotumour.[8]

IgG4-RD may present as a tumour-like enlargement of organs, characterised by lympho-plasmacytic invasion of IgG4-positive plasma cells and often raised serum IgG4 concentration.[9] The histopathological findings are an important hallmark of IgG4-RD diagnosis. The features include infiltration of lymphocytes and plasma cells, IgG4-positive plasma cells of more than 10 per high-power field (hpf), IgG4-positive plasma cells/IgG-positive cells ratio greater than 40%, and fibrosis such as storiform fibrosis or obliterative phlebitis. A serum IgG4 level greater than 135 mg/dL is another supporting criterion for diagnosing IgG4-RD.[10] The management of IgG4-RD often involves the induction of corticosteroids. A maintenance dose may be required to prevent relapse, and monoclonal antibodies such as rituximab show promising results.[11]

HL and IgG4-RD are distinct pathological entities with overlapping features, such as lymphadenopathy and constitutional symptoms. We reported a diagnostically challenging case that was initially managed as probable IgG4-RD, but subsequently confirmed to be HL following a repeat biopsy. This case highlights the importance of maintaining a high index of suspicion and performing repeat biopsy in atypical manifestations of presumed IgG4-RD.

CASE REPORT

A 29-year-old man presented with a history of right-sided neck swelling for the past 8 years. This was associated with a profound weight loss of about 26 kg over the last year. He denied systemic symptoms such as shortness of breath, bone pain, or altered bowel habits. The swollen neck measured 8cm x 15cm and was non-tender. The neck magnetic resonance imaging (MRI) revealed multiple well-encapsulated, lobulated, and matted right cervical lymphadenopathy. The bone marrow aspirate biopsy showed a reactive plasmacytosis without marrow infiltration or the presence of acute leukaemia. The excisional lymph node biopsy showed many IgG4+ plasma cells, up to 70 cells per hpf, and the IgG4+/IgG+ plasma cell ratio is about 20% (Figure 1). However, there is no stromal fibrosis, granuloma, obliterative phlebitis, or malignant cells. The serum IgG4 subclass was raised to 258 mg/dL, and the serum IgG1 was raised to 3630 mg/dL. The serum and urine electrophoresis did not reveal any paraprotein bands. Based on the Revised Comprehensive Diagnosis (RCD) 2020, he did not fit into a typical 'probable or possible IgG4-RD' diagnosis. The patient was started on glucocorticoids (1 mg/kg) and azathioprine (2 mg/kg) to look for a response. Despite 3 months of corticosteroids and azathioprine treatment, his condition did not improve, and the serum globulin remained elevated.

This was when a repeat biopsy was taken, which revealed proliferation of Hodgkin and RS cells, surrounded by inflammatory cells, namely lymphocytes, eosinophils, plasma cells,

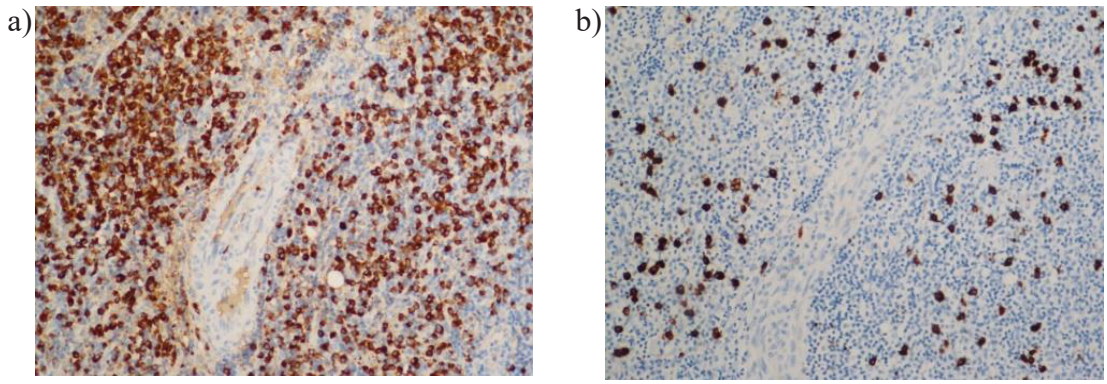

Figure 1. The immunostaining of the excised lymph node biopsy shows (a) IgG+ plasma cells and (b) IgG4+ plasma cells.

and histiocytes (Figure 2). The Hodgkin and RS cells are CD30+, focal CD15+, Ki-67+, and dimPAX5+. The CD3, CD20, and CKAE1/AE3 were all negative.

An Epstein-Barr virus RNA in situ hybridisation (EBER-ISH) was also performed, but it was negative (Figure 3). A diagnosis of MCHL was made, and the ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) chemotherapy regimen was initiated. He achieved remission after completing 6 cycles of ABVD, but relapsed within 9 months. Subsequently,

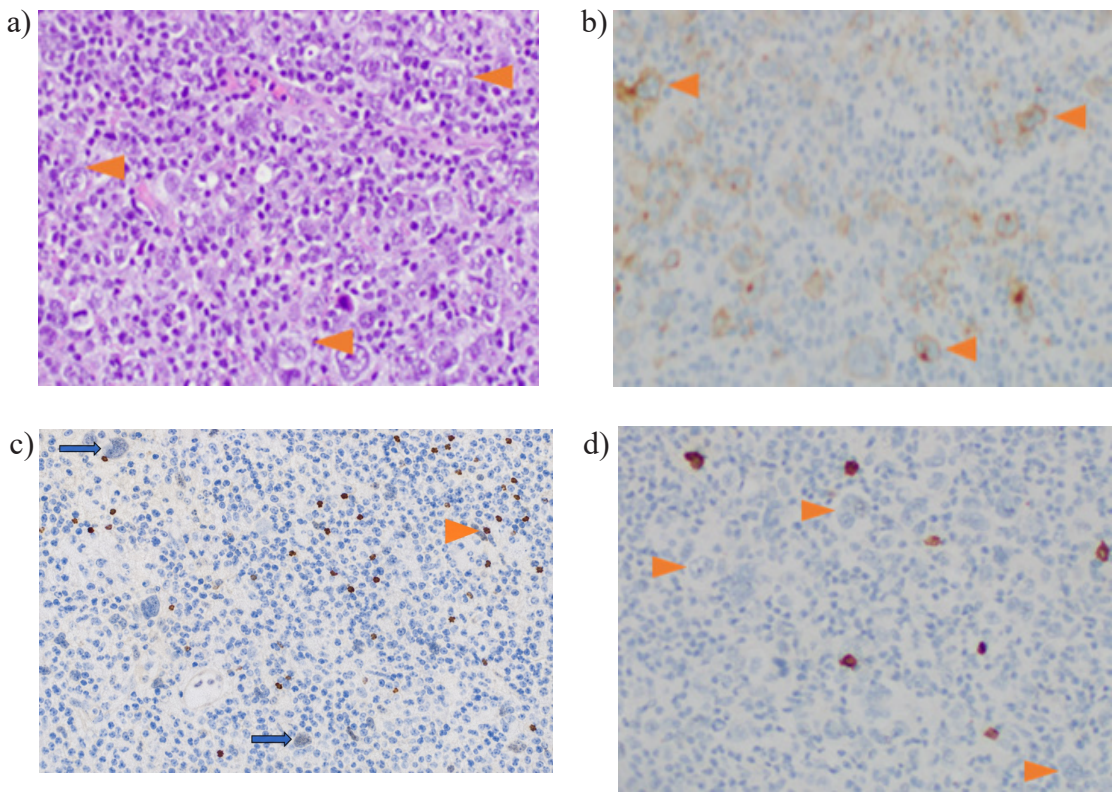

Figure 2. Histopathology of the repeat lymph node biopsy (200×), a) Arrowhead showing Reed-Sternberg (RS) cells (H&E stain), b) Arrowhead showing CD30 positive RS cells, c) RS cells showing dim positive PAX5 (blue arrow), with brown stained PAX5 positive B-cells (arrowhead), d) Arrowhead showing RS cells lacking CD20 (CD20 negative RS cells)

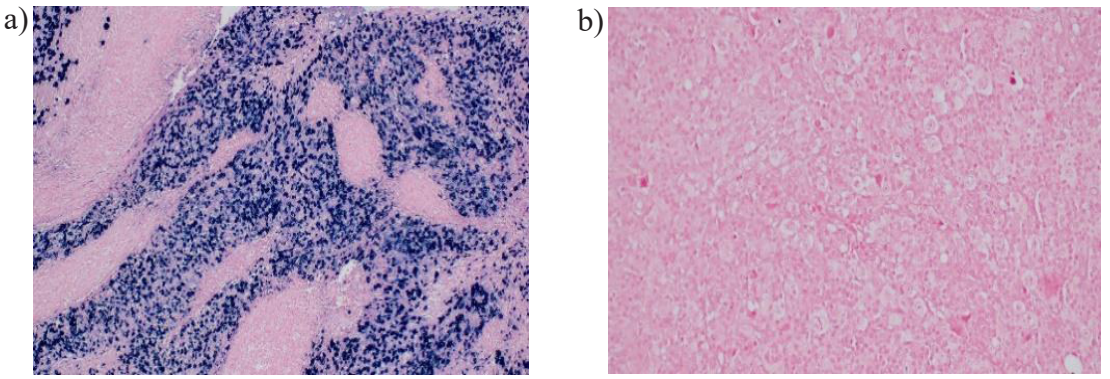

Figure 3. The Epstein-Barr virus RNA-in-situ hybridisation (EBER-ISH) of (a) Positive Control and (b) Patient.

a salvage chemotherapy regimen with ICE (ifosfamide, carboplatin, etoposide) was given in a total of 3 cycles. He then achieved complete remission (CR) and is currently awaiting stem cell transplantation. His neck swelling subsided, and serum globulin levels normalised.

DISCUSSION

IgG4-RD is a chronic, fibroinflammatory lymphoproliferative disorder characterised by infiltration of IgG4+ plasma cells and fibrotic changes in affected tissues, occasionally accompanied by a raised serum IgG4. However, elevated serum IgG4 levels may also be seen in other conditions, such as atopic diseases, pancreatic malignancy, infections, and can also be raised in about 5% of the normal population.[12] Other supportive features suggestive of IgG4-RD include polyclonal hypergammaglobulinemia, hypocomplementemia, elevated erythrocyte sedimentation rate (ESR), and serum IgE levels.[13-15] None of these was seen in this patient except for hypergammaglobulinemia. Given that IgG4-RD is an evolving condition, the biopsies obtained in the initial stages may not represent the histopathological characteristics of the disease.[16] In this case, the initial biopsy did show some features suggestive of IgG4-RD but did not fit the RCD 2020 criteria. Based on the criteria, if there is a single organ involvement, lymph node swelling is omitted.[7] There was also an absence of typical tissue fibrosis, and the IgG4+/IgG+ plasma cell ratio was not greater than 40%. Additionally, the biopsy was also negative for other conditions, such as malignancy, so a trial of glucocorticoids was initiated.

Glucocorticoids are the mainstay of treatment for IgG4-RD, and most respond well to this treatment. However, due to the potential for toxicity, they are often combined with disease-modifying anti-rheumatic drugs (DMARDs), such as cyclophosphamide or azathioprine. Combination therapy has also been shown to lower relapse rates and prolong remission.[17,18] In this patient, however, three months of treatment with glucocorticoids and azathioprine resulted in no significant clinical improvement.

The subsequent follow-up and a decision to repeat the lymph node biopsy after 3 months of combined therapy revealed proliferation of Hodgkin cells and RS cells surrounded by inflammatory cells. The immunohistochemistry (IHC) of RS cells is typically CD30 and CD15 positive, whereas CD20 is negative. They can also be positive for PAX5, and Ki-67.[7,19] A subtype of MCHL was finally diagnosed for this patient. MCHL is a type of classical HL, seen in about 15-30% of HL cases. MCHL typically occurs in the elderly, is associated with EBV, and often affects the bones, bone marrow, or subdiaphragmatic lymph nodes.[20] While the overall histological architecture supports a diagnosis of MCHL, the clinical presentation (young adult, supradiaphragmatic) and EBER-negativity are atypical for this subtype. We hypothesize that this case represents a distinct biological variant of MCHL, or potentially the 'cellular phase' of Nodular Sclerosis, that arises through EBV-independent mechanisms.

The discrepancy between the first and the second biopsy in this case could have been most likely due to the intrinsic heterogeneity of the pathology. The initial biopsy could have represented a region rich in IgG4+ reactive inflammation while masking the underlying malignancy cells. An observation by Nowak *et al*. (2020) among their nodular sclerosing

Hodgkin lymphoma (NSHL) cases revealed a higher incidence of IgG4+ plasma cells in approximately 21% of the NSHL cases, fulfilling the diagnostic criteria for IgG4-RD. This feature has the potential to result in missed diagnosis and pose a diagnostic pitfall for pathologists.[21]

The first line of treatment for cHL is ABVD or an escalated BEACOPP regimen (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine, Prednisolone), depending on the stage of the disease. The standard of care may vary between countries, and there could be some limitations due to their toxicities.[22] Although the ABVD regimen yields an overall survival rate of 80-90% in HL, approximately 30-40% of the patients will experience relapse within the first two years post-treatment, often requiring salvage therapy.[23] This patient relapsed nine months after the first-line chemotherapy. He received salvage chemotherapy with ICE (Ifosfamide, carboplatin, and etoposide). An autologous stem cell transplantation following a salvage therapy has long served as a standard approach, achieving a cure rate of approximately 50% among the relapsed and refractory HL cases.[24-26]

CONCLUSION

Although the initial findings were suggestive of IgG4-RD, the repeated biopsy ultimately confirmed a diagnosis of HL. This case underscores the importance of identifying the potential overlap between the two clinical entities, as misinterpretation may delay diagnosis and timely medical or surgical intervention. It also emphasises the need to vigorously investigate the presence of malignant cells by morphology in cases where IgG4-RD is suspected. Given that IgG4-RD demonstrates a high propensity for mimicking various other inflammatory and neoplastic conditions, the performance of a repeat biopsy is strongly warranted in cases that lack therapeutic response following an initial diagnosis. Clinico-pathological correlation is essential for resolving challenging and ambiguous diagnoses.

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