

# Waldenström Macroglobulinemia and Chronic Myelomonocytic Leukemia: Case Report and Literature Review

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**Abstract:** As hematological tumor patients are surviving long-term, the long-term toxicities of therapeutic regimens have become increasingly evident. The coexistence of two hematological tumors in the same patient is extremely rare and typically shows an aggressive clinical course and unsatisfactory prognosis. In the present case, we describe the case of a 64-year-old man who was admitted to the hospital because of fatigue. Biochemical showed an elevated monoclonal immunoglobulin M (IgM) at 37g/L. Next Generation Sequencing (NGS) analysis revealed MYD88<sup>L265P</sup> mutation, CXCR4 wild type. In August 2020, he was diagnosed with Waldenström macroglobulinemia (WM) and underwent six cycles of chemotherapy with bendamustine, zanubrutinib, and rituximab. However, he was admitted to the hospital in December 2022 following six-month history of Leukocytosis. Bone marrow (BM) flow cytometry (FCM) showed increased MO1 monocytes. Molecular studies were positive for TET2 mutations. He was finally diagnosed with WM and chronic myelomonocytic leukemia (CMML). Then he accepted hematopoietic stem cell transplantation (HSCT). Unfortunately, after 6 months, the patient died as a consequence of severe pulmonary infection.

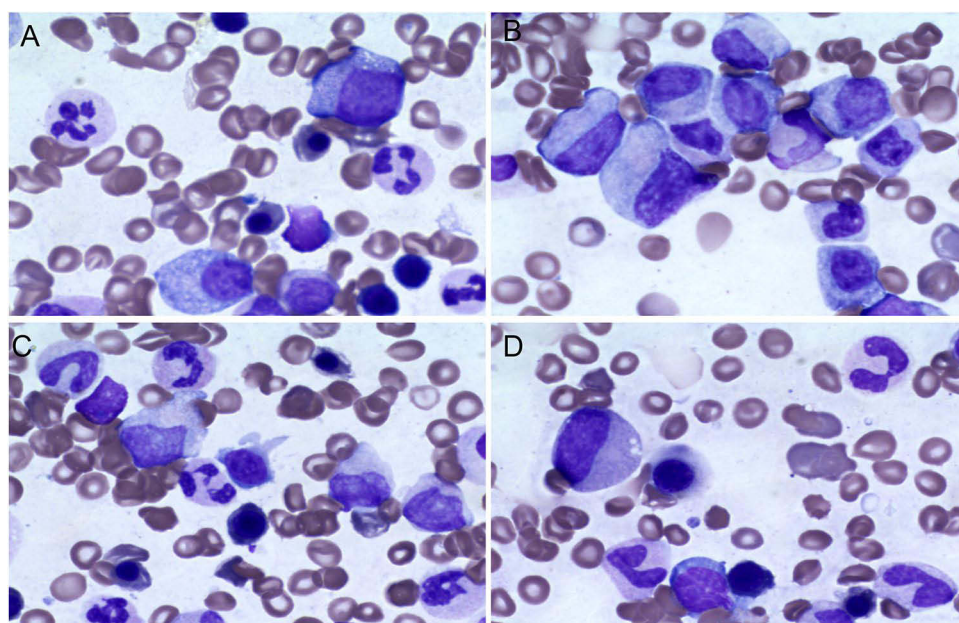
**Keywords:** Waldenström macroglobulinemia, chronic myelomonocytic leukemia, lymphoproliferative disorder, hematopoietic stem cell disorder, hematopoietic stem cell transplantation

## Introduction

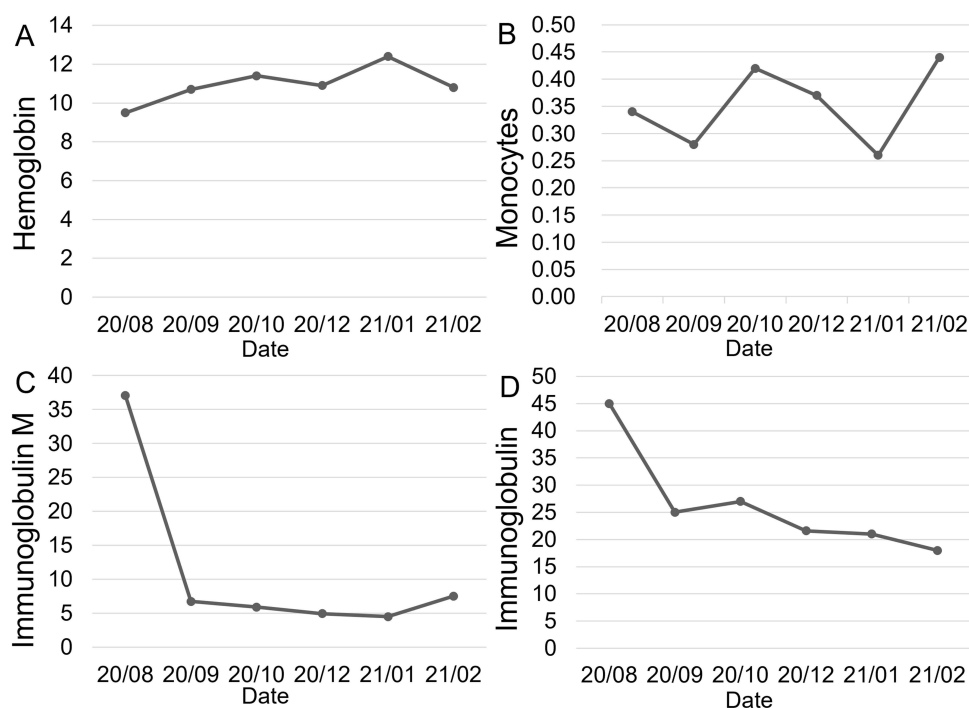
WM is a chronic B lymphoproliferative disorder distinguished by the presence of IgM in the bone marrow, lymph nodes, and spleen.<sup>1</sup> WM includes a wide range of conditions that have different causes and exhibit a varied clinical progression, with some cases being extremely slow-growing while others can escalate quickly.<sup>1,2</sup> The clinical manifestations of active WM are highly variable and may include symptoms or end-organ damage associated with cytopenias, hyperviscosity, amyloid light/heavy chain amyloidosis (ALH), cryoglobulinemia, histologic transformation (HT), and peripheral neuropathy, among other complications.<sup>1–3</sup> Common clinical symptoms include systemic manifestations like anemia, fatigue, and anorexia. CMML, a clonal hematopoietic stem cell disorder, exhibits overlapping features of myelodysplastic syndromes and myeloproliferative neoplasms.<sup>4,5</sup> Patients typically present with persistent monocytosis and dysplasia.<sup>4</sup> As patients with lymphoid neoplasms (LNs) are surviving for longer periods, the late toxicities of treatment are becoming increasingly evident. These toxicities can result in the onset of secondary hematological malignancies such as therapy-related myelodysplastic syndrome (tMDS) or acute myeloid leukemia (AML), which are typically fatal complications associated with chemotherapy, particularly alkylating agents, topoisomerase II inhibitors, and platinum compounds.<sup>6,7</sup> Here we report a patient suffer from WM and CMML who accepted HSCT.

## Case Report

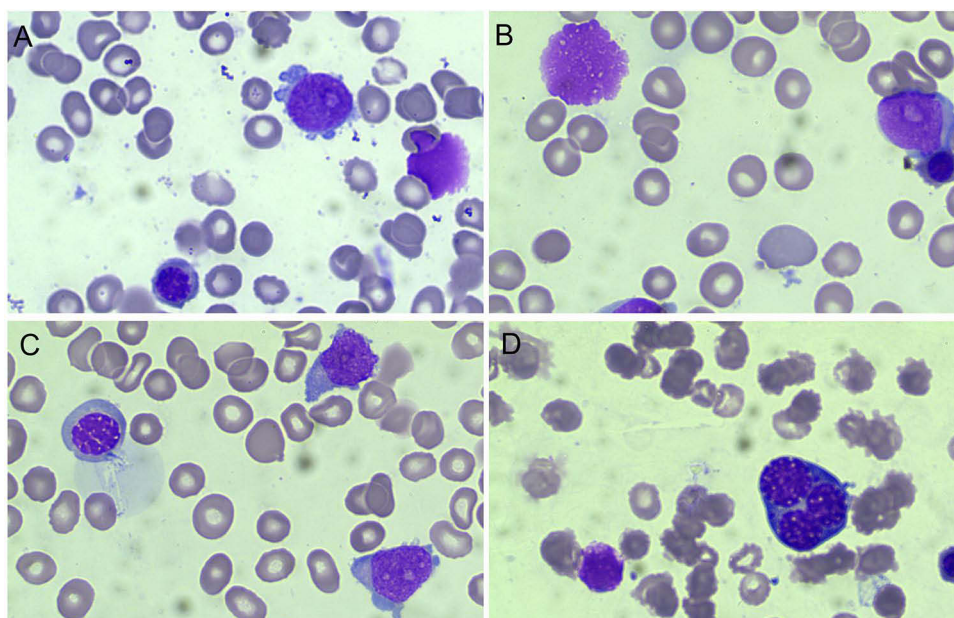
The patient, a 64-year-old man, was admitted to the Hematology Department of Jiangsu Provincial People's Hospital in August 2020 who presented with fatigue but no fever or night sweats. Physical examination did not reveal enlarged lymph nodes, splenomegaly, or hepatomegaly. Laboratory findings indicated mild anemia (Hb 10.4 g/dL), leukopenia (WBC  $5.8 \times 10^9/L$ ), and thrombocytopenia (platelets  $181 \times 10^9/L$ ). The absolute monocyte counts  $0.34 \times 10^9/L$  and 5.2% monocytes. Biochemical showed globulin at 45g/L,  $\beta_2$ -microglobulin at 27.2mg/L, and an elevated monoclonal IgM at 37g/L. The peripheral blood smear suggested 12% atypical lymphocytes and rouleaux formation. The bone marrow smear suggested 2% lymphoplasmacytic cells (Figure 1). FCM suggested that atypical monoclonal lymphocytes occupied about 34% of nuclear cells, expressing CD45, CD19, CD20, CD22, CD79b, IgM, CD38, CD200, CD81, CD148, CD49d, Kappa. Bone marrow biopsy diagnosed non-Hodgkin lymphoma (mature small B cell type). NGS analysis revealed MYD88<sup>L265p</sup> mutation, CXCR4 wild type. FDG-PET scanning revealed disseminated lymphadenopathy. Combined with the clinical manifestations and related tests, the diagnosis of WM was made. Six cycles of chemotherapy with bendamustine, zanubrutinib and rituximab (Figure 2). Following six cycles of treatment, a repeat bone marrow aspiration and biopsy were performed to evaluate the patient's response. The results indicated a very good partial response (VGPR). However, the patient was readmitted to the hospital due to severe atrial fibrillation and subsequently followed the doctors' recommendation to discontinue zanubrutinib. He then underwent radiofrequency treatment. Continued monitoring of routine blood count showed mild anemia. His serum IgM level remained stable at 7.5 mg/dL and the mutation of MYD88<sup>L265p</sup> was no longer found. After 11 months following the completion of treatment, the patient continued to experience monocytosis that either persisted or gradually worsened. Due to the potential of CMML, he was admitted for further evaluation in December 2022. During the physical examination, his vital signs were within normal range, his abdomen was soft and not distended, and there were no palpable signs of lymphadenopathy or splenomegaly. Laboratory tests revealed Hb 10.4 g/dL, WBC  $10.95 \times 10^9/L$ , the absolute monocyte counts  $1.17 \times 10^9/L$  and 10.6% monocytes, platelets  $103 \times 10^9/L$ . Biochemical showed globulin at 18g/L, monoclonal IgM at 6.5g/L. A review of his medical records from the past 11 months revealed a progressive increase in leukocytosis, particularly monocytosis. A diagnostic BM aspirate smear revealed hypercellularity, trilineage dysplasia, monocytosis (Figure 3). At the same time, molecular studies were positive for TET2 mutations. Additionally, BM FCM showed increased MO1 monocytes (Figure 4). Then he received frontline treatment with azacitidine and venetoclax regimen repeated every 4 weeks, for a total of 11 courses initial, followed by decitabine, homoharringtonine and venetoclax regimen 1 course for CMML. In September 2023, after



**Figure 1** Patient's bone marrow smear. (A-D): Under high magnification, these lymphoid plasma cells are small and irregularly shaped; the nucleus is round, lymphatic, and eccentric; the cytoplasm is abundant and dark grey-blue (Wright-Giemsa stain. Magnification $\times 1000$ ).



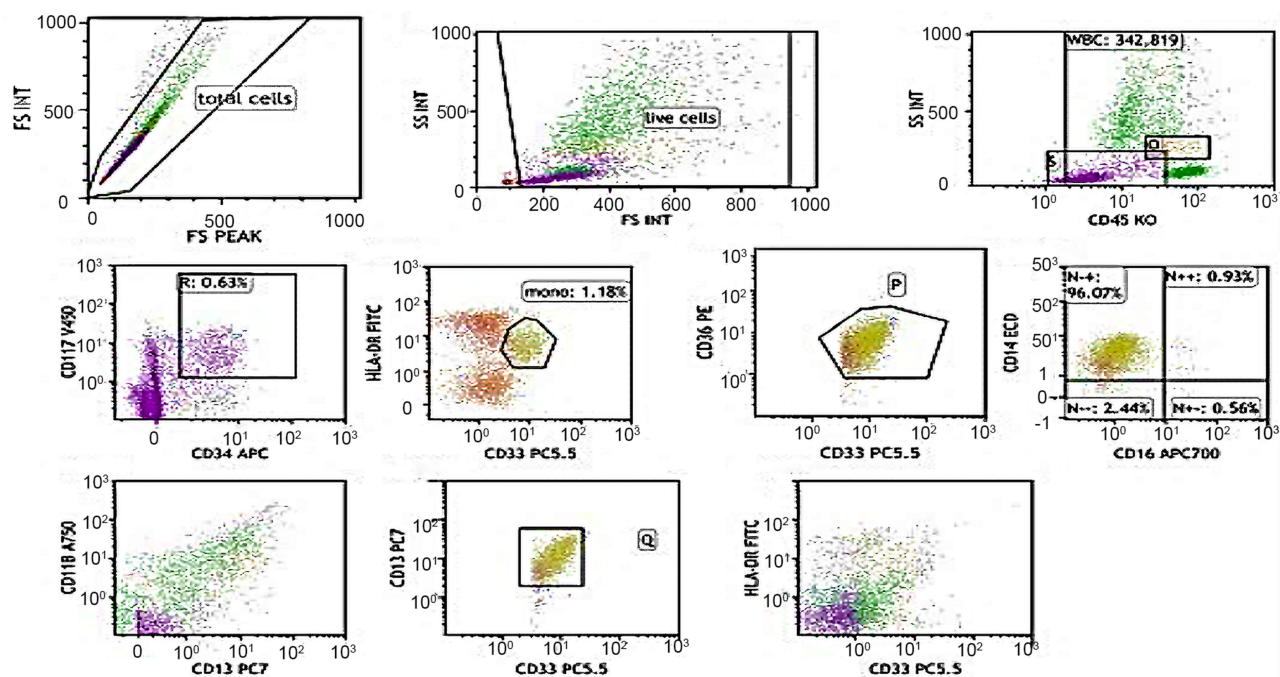
**Figure 2** Evolution of biological parameters after treatment. Hematological parameters in peripheral blood during treatment for WM are reported, referred to hemoglobin, measured in g/dL (**A**), absolute monocyte count (**B**), IgM measured in g/L (**C**), and Immunoglobulin, g/L (**D**).



**Figure 3** Patient's bone marrow smear. (**A–D**): Bone marrow aspirate showed nuclear irregularity in erythroids, dysplasia in granulocytic and megakaryocytic cell lineages (Wright-Giemsa stain. Magnification×1000).

completing the relevant examinations, the patient, who was O Rh(D)-positive, underwent HSCT. The donor was an unrelated, matched B Rh(D)-positive male. The conditioning regimen included fludarabine, thiopeta, and targeted busulfan. Engraftment was successful; however, the patient unfortunately succumbed to a severe pulmonary infection six months later.





**Figure 4** Bone marrow flow cytometric analysis. Flow cytometry of bone marrow showing increased CD14+/CD16− classic MOI monocytes (94%).

## Discussion

WM, a rare mature B-cell lymphoplasmacytic lymphoma, is characterized by clonal bone marrow infiltration of lymphoplasmacytic cells and the presence of IgM.<sup>1</sup> Certain individuals might be asymptomatic or show signs of “smoldering” Waldenström macroglobulinemia (SMW) upon diagnosis, whereas others may display clinical manifestations due to increased IgM serum concentrations and infiltration of lymphoplasmacytic cells in the bone marrow, lymph nodes, and spleen (symptomatic WM).<sup>8</sup> Anemia, fatigue, and anorexia are frequently seen clinical features.<sup>2,6</sup> The most prevalent somatic abnormality in WM is a gain of function mutation of the MYD88 gene, observed in 93–97% of cases.<sup>9,10</sup> Co-mutations in CXCR4 are present in 30–40% of patients.<sup>10</sup> TP53 is altered in 20% to 30% of patients with WM, particularly those previously treated.<sup>11</sup> This particular patient was hospitalized due to fatigue. He was diagnosed with WM based on the presence of IgM- $\kappa$  type monoclonal protein and the identification of lymphoplasmacytic cells infiltrating the bone marrow on biopsy. WM remains an incurable chronic malignancy, and standardized global treatment guidelines are currently lacking. The primary objective of therapy is to manage symptoms and reduce tumor burden, although achieving a complete response (CR) with existing treatments is challenging. While a watch-and-wait strategy may be suitable for patients without symptoms, treatment is warranted for those experiencing disease-related anemia, thrombocytopenia, significant adenopathy, organomegaly, symptomatic hyperviscosity, amyloidosis, peripheral neuropathy, cryoglobulinemia, cold-agglutinin disease, or transformation of the disease.<sup>2,9,12</sup> Commonly used agents for treating WM include monoclonal antibodies, alkylating agents, proteasome inhibitors, and Bruton Tyrosine Kinase inhibitors (BTKi).<sup>12</sup> Patients with immune-related cytopenia or symptomatic adenopathy or organomegaly will benefit from rituximab-based chemo-immunotherapy, the standard first-line treatment that can rapidly decrease tumor burden. Plasmapheresis should be considered for patients with hyperviscosity, symptomatic cryoglobulinemia, and severe hemolysis due to cold agglutinin disease.<sup>2,13</sup> The incidence of neuropathy with bortezomib-based regimens necessitates careful consideration, prompting consideration of BTKi in specific patients with IgM-related neuropathy. BTK, a vital non-receptor tyrosine kinase, is crucial in the development, maturation, differentiation, and proliferation of B lymphocytes.<sup>10</sup> MYD88 serves as an adaptor protein, engaging with Toll-like receptors and interleukin (IL)-1 receptors, and undergoes dimerization following receptor activation. Mutations in MYD88 lead to the activation of BTK via hematopoietic cell kinase (HCK), which is a member of the SRC family.<sup>10,14</sup> Covalent BTK inhibitors (cBTKi) produce major responses in 70% to 80% of patients with WM.<sup>11</sup> Additionally, activating mutations in CXCR4, which

encompass both nonsense and frameshift variants, have been identified in 30–40% of individuals diagnosed with WM.<sup>11,15</sup> CXCR4 co-mutations are associated with lower overall response rate (ORR) and less durable responses with BTKi.<sup>15</sup> MYD88 and CXCR4 mutations have prognostic and therapeutic implications, impacting response depth, time to major response, and progression-free survival (PFS).<sup>11,16</sup> Zanubrutinib, a potent selective next-generation covalent BTKi approved for adult WM patients in several countries.<sup>16,17</sup> In the Phase III ASPEN trial, zanubrutinib was directly compared with ibrutinib, showing that it has either comparable or even enhanced efficacy.<sup>15–17</sup> Despite the substantial improvement in outcomes and quality of life with BTKi treatment, patients with a history of cardiovascular disease exhibit a high incidence of severe atrial fibrillation.<sup>11,15</sup> CMML is a malignant hematopoietic stem cell disease that straddles the intersections of myeloid proliferative neoplasms (MPN) and myelodysplastic syndromes (MDS). Within three to five years, 15–20% of cases of CMML may develop into leukemia.<sup>4,5</sup> The etiology and pathophysiology of CMML remain largely unknown; however, it appears to be complex and may be associated with alterations in genetic, molecular, immunological, and microenvironmental factors across different individuals.<sup>4</sup> Notably, these patients exhibit a high frequency (40% to 50%) of mutations in TET2, SRSF2, and ASXL1.<sup>18</sup> Among the various epigenetic factors, truncating variants of ASXL1 are linked to negative outcomes in CMML, characteristics of proliferative diseases, and a lack of responsiveness to epigenetic treatments.<sup>4,19</sup> The new WHO classification for 2022 has updated the current diagnostic criteria for CMML, adding prerequisite and supporting criteria. Although the threshold for continuous absolute monocytosis has been reduced from 1000/ $\mu$ L to 500/ $\mu$ L, monocytes must still make up more than 10% of WBC.<sup>4,20</sup> Furthermore, it has been determined that the blast-based subgroup of CMML-0 has no prognostic significance, hence it has been eliminated.<sup>21</sup> As per Dr. Seligmoglu-Buet's report, the WHO's current 500/ $\mu$ L cutoff for CMML prediction is weaker than the presence of > 94% of CD14+CD16– classical monocytes (MO1s) in peripheral blood.<sup>22</sup> Along with hypomethylating agents (HMA), HSCT, and supportive measures, the primary treatment strategies for CMML have changed significantly, leading to notable improvements in survival after CMML. The hematological responses observed frequently lack durability and do not considerably change the biology of the disease or its progression to AML. This is notwithstanding the dramatic alterations in DNA methylation induced by HMA, which suggest a potential epigenetic restoration of normal hematopoiesis. Additionally, recent findings indicate that mutant progenitor cells also play a role in the restoration of hematopoiesis upon exposure to HMA.<sup>4,23</sup> Allogeneic HSCT represents the sole curative approach for CMML, with reported five-year overall survival rates of 30–40% post-transplant.<sup>24,25</sup> It is still uncertain if debulking could gain advantages from bridging treatment prior to HSCT; additionally, the application of HMAs in the pretransplant context continues to be a matter of debate.<sup>4,25</sup> Historically, survivors of common LNs have been found to have an increased risk of developing tMDS/AML.<sup>26</sup> The occurrence of tMDS/AML is a well-established rare but often fatal adverse outcome in patients treated with chemotherapy, including specific alkylating agents, topoisomerase II inhibitors, and platinum compounds for LNs.<sup>27</sup> Despite its rarity, the 8-month median survival after a tMDS/AML diagnosis highlights the high fatality rate associated with this rare outcome. Patients with therapy-related chronic myelomonocytic leukemia (t-CMML), when compared to those with de novo cases, are more likely to exhibit cytogenetic abnormalities with higher risk karyotypic stratification and a shorter median overall survival (OS).<sup>4,28</sup> The exact pathogenesis of the co-occurrence of myeloproliferative and plasma cell disorders remains unclear. The absence of overlapping mutation profiles between WM and CMML suggests that these two hematological malignancies are not directly related to each other. While the leukemogenic potential of many newer agents is still not fully understood, it is worth noting that mutations in NPM1, IDH2, ASXL1, and spliceosome genes were anticorrelated with agents that are commonly associated with t-MNs (alkylators, anthracyclines, and topoisomerase inhibitors).<sup>7</sup> Currently, there is no standardized treatment approach for managing lymphoma combined with myeloid leukemia, and certain patients may benefit from individualized, risk-adapted treatment strategies that allow for therapy deintensification.<sup>29</sup> For nontransplantable patients, separate treatment plans are necessary for addressing both diseases.<sup>30</sup>

## Conclusion

The coexistence of WM and CMML is exceedingly rare and presents significant clinical management challenges in managing these distinct malignancies. Here, we present a case of a patient diagnosed with both hematological malignancies, treated for each malignancy separately, and ultimately undergoing HSCT. This case underscores the importance of close monitoring and consideration of long-term adverse effects when managing patients with indolent lymphomas, particularly WM. It is crucial to take into account late complications and carefully weigh the risks and

benefits of treatment options. As therapeutic strategies for multiple hematological malignancies continue to advance, future studies with extended follow-up, novel therapies, and comprehensive clinical data will be essential for assessing the risks of tMDS and AML and guiding risk assessments for specific treatment regimens.

## Ethics Committee

The study protocol was approved to carry out by the Ethics Committee of The First Affiliated Hospital With Nanjing Medical University, Jiangsu Province Hospital, and institutional approval was not required to publish the case details. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. The study was performed in accordance with the principles of the Declaration of Helsinki. Acknowledgment We thank all the medical care personnel involved in the treatment of this patient, especially Dr. Ping Chu. She was involved in the surgery and treatment. Disclosure The authors report no conflicts of interest related to this work.

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## Disclosure

The authors report no conflicts of interest in this work.

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