Complete renal and haematological remission in a case of mantle cell lymphoma associated paraneoplastic focal segmental glomerulosclerosis with ibrutinib: a case report and review of literature

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Background: Mantle cell lymphoma (MCL) accounts for 7% of adult mature B cell non-Hodgkin lymphomas (NHLs). Paraneoplastic focal segmental glomerulosclerosis (FSGS) is an exceedingly rare association of MCL. There is limited evidence on the outcomes of lymphoma associated paraneoplastic renal syndromes who are treated with Bruton tyrosine kinase inhibitors. We describe a rare case of MCL associated FSGS who was successfully treated with a chemotherapy free regimen of single agent ibrutinib and continues to be in sustained complete remission with respect to lymphoma and FSGS-related proteinuria at a follow-up of 2 years.

Case Description: A 73-year-old gentleman presented with 2-month history of bilateral pedal oedema with frothy urine. Examination revealed generalized lymphadenopathy with hepatosplenomegaly. Twenty-four-hour urine protein was 11 grams/total volume, suggesting nephrotic syndrome. There were atypical circulating lymphocytes in the blood. Flowcytometry and cytogenetic studies from bone marrow aspirate and histopathology of lymph node biopsy confirmed the diagnosis of MCL. Kidney biopsy revealed FSGS. The patient was treated with ibrutinib 560 mg once daily considering his age and preference for oral therapy. At the end of two years of follow-up the patient is in complete remission for both MCL and FSGS.

Conclusions: Our case highlights that FSGS can be a rare paraneoplastic renal manifestation of MCL. Bruton tyrosine kinase inhibitors can be safely used effectively in patients with paraneoplastic lymphoma associated FSGS.

Keywords: Mantle cell lymphoma; focal segmental glomerulosclerosis; ibrutinib; case report

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Introduction

Hematologic malignancies are associated with a number of paraneoplastic glomerular, tubulointerstitial and renovascular diseases. Paraneoplastic renal manifestations can be the presenting clinical manifestation of an underlying malignancy (1). Minimal change disease (MCD) associated with Hodgkin lymphoma is a classic example of paraneoplastic glomerulonephritis. Membranoproliferative glomerulonephritis and membranous nephropathy associated with chronic lymphocytic leukemia, hairy cell leukemia and non-Hodgkin lymphoma (NHL) constitute other examples of chronic lymphoproliferative disorder (CLPD) associated paraneoplastic glomerulonephritis (2). Paraneoplastic focal segmental glomerulosclerosis (FSGS) has been rarely described in the setting of lymphoreticular malignancies.

Mantle cell lymphoma (MCL) is one of the aggressive varieties of B-cell NHL with high relapse rate and a median survival of 12–15 years (3). There are sporadic reports of FSGS in the background of MCL treated with chemoimmunotherapy with variable outcomes (4,5). Herein, we describe a rare case of MCL associated FSGS who was successfully treated with a chemotherapy free regimen of single agent ibrutinib and continues to be in sustained complete remission with respect to lymphoma and FSGS related proteinuria at a follow-up of 2 years. We present this case in accordance with the CARE reporting checklist (available at https://aol.amegroups.com/article/view/10.21037/aol-22-21/rc).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 73-year-old male patient presented to the outpatient department with history of progressive pedal oedema along with frothy urine of 2-month duration. On examination, patient had an ECOG Performance Status 3 with conjunctival pallor and bilateral pitting pedal oedema extending up to the knees. There were palpable bilateral cervical, axillary, and inguinal lymph nodes of size ~3×3 cm. Liver was palpable 2 cm below the right costal margin and spleen was palpable 4 cm below the left costal margin.

Investigations revealed hemoglobin of 9.1 g/dL (normal range, 13–16 g/dL), total leukocyte count of 7,700 cells/µL (normal range, 4,000–11,000/µL), platelet count 334,000/µL. The differential count had 22% polymorphs, 57% lymphocytes, 8% monocytes, 13% eosinophils with 12% atypical lymphocytes (*Figure 1A*). Serum creatinine was elevated to 1.6 mg/dL (normal range, 0.5 to 1.2 mg/dL). Serum total protein was 4.7 g/dL (normal range, 6.4–8.3 g/dL) with albumin of 1.8 g/dL (normal range, 3.4–4.8 g/dL). Twenty-four-hour urine protein was 11 g with predominant albuminuria. Lactate dehydrogenase was raised to 470 U/L (upper limit of normal 248 U/L). Serology for hepatitis B, hepatitis C, human immunodeficiency virus, anti-nuclear antibody, and anti-phospholipase A2 receptor antibody was negative.

Contrast enhanced computed tomography scan of chest and abdomen showed multiple sub-centimetric lymph nodes in cervical and supraclavicular regions, bilateral para-hilar lymphadenopathy, multiple retroperitoneal, inguinal, and external iliac lymph nodes largest 1.8 cm in size. Bone marrow trephine biopsy imprint smear showed aggregates of atypical lymphocytes (*Figure 1B*). Bone marrow trephine biopsy showed multiple nodular infiltrates (*Figure 1C-1E*). On immunohistochemistry the lymphoid nodules were positive for CD 20 and negative for SOX11 with a with a Ki67cell proliferation index ~10%. On multicolor flowcytometry, gated CD19 positive events (11% of viable cells) showed positivity for CD5, CD20, CD79b and surface lambda light chains. They were negative for CD10, CD23, CD43 and surface kappa light chains (*Figure 2*). Fluorescent *in-situ* hybridization using dual color break apart probe showed *CCND1* rearrangement (Metasystems GmBH; Germany) and was negative for del17p (*Figure 3*). These findings were consistent with MCL. Lymph node biopsy from right axillary node also showed infiltration by CD20, CD5 and Cyclin D1 positive, intermediate sized atypical lymphoid cells consistent with the diagnosis of MCL.

Kidney biopsy showed one of the glomeruli to be globally sclerosed. One other glomerulus showed focal and segmental sclerosis in the para hilar region and synechiae formation. The rest of the glomeruli were unremarkable (*Figure 4A,4B*). Direct immunofluorescence for immunoglobulin and complement deposits on the kidney tissue was negative. The Congo red stain for amyloid was negative. Based on these findings, he was diagnosed to have MCL Stage IV B with a high-risk Mantle Cell Lymphoma

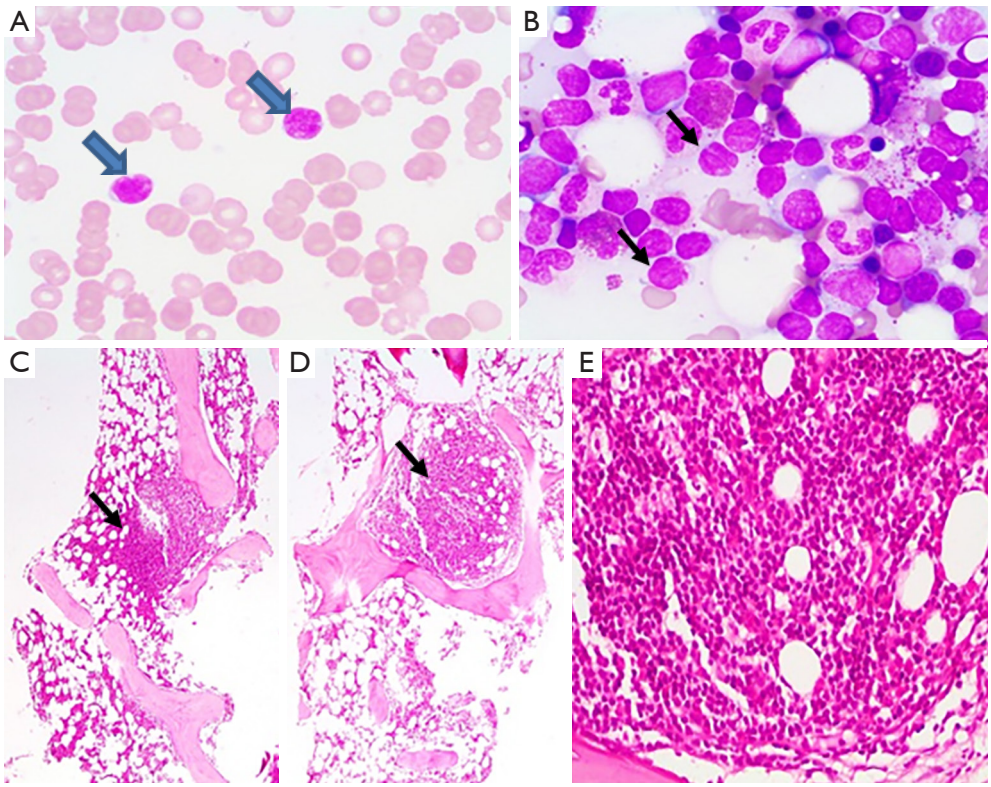

Figure 1 Peripheral blood and bone marrow findings. (A) Peripheral blood showing circulating atypical lymphocytes with nuclear membrane indentation (thick arrow) (May Grunwald Giemsa stain, magnification ×100); (B) bone marrow trephine imprint smear showing aggregate of atypical lymphocytes (May Grunwald Giemsa stain, magnification ×100); (C,D) bone marrow trephine biopsy sections showing multiple nodular infiltrate of lymphoma (arrows) (hematoxylin and eosin stain, magnification ×4); (E) high power view showing small to intermediate sized atypical lymphocytes (hematoxylin and eosin stain, magnification ×40).

International Prognostic Index (MIPI) score (7.5) and paraneoplastic FSGS.

Considering the ongoing COVID-19 pandemic, patient's age, and his preference for oral therapy he was started on continuous ibrutinib 560 mg per oral daily without any steroids or anti-CD20 directed monoclonal antibodies. An interim F18-fluorodeoxyglucose (FDG) positron emission tomography-computer tomography (PET-CT) scan analysis at 6 months of therapy showed no definite PET evidence of clinically significant abnormal hypermetabolism anywhere in the body. Besides, there was gradual decrease in 24-hour urine protein levels of the patient over a period of 2 years from 11 to 0.15 g (*Figure 5*). There was also rapid normalization of serum creatinine after the initiation of therapy (*Figure 6*). At the end of 2 years of follow-up he continues to remain in complete remission for both MCL and nephrotic syndrome due to FSGS.

Discussion

Renal manifestations in MCL are most commonly seen as a result of direct infiltration of the kidney by clonal lymphoid cells, tumor lysis syndrome or nephrotoxic chemotherapeutic drugs. Paraneoplastic membranoproliferative glomerulonephritis and FSGS are rare renal manifestations associated with MCL. *Table 1* summarizes the previously published cases of paraneoplastic glomerulonephritides in MCL (4-11). In the two previous cases of FSGS associated with MCL described by Wong *et al.* and Hindocha *et al.*, FSGS predated the diagnosis of MCL. In both these cases, FSGS directed immunosuppression was not effective, however lymphoma directed chemo-immunotherapy [rituximab, cyclophosphamide, vincristine, prednisolone (R-CVP) and rituximab, cyclophosphamide, hydroxydaunorubicin

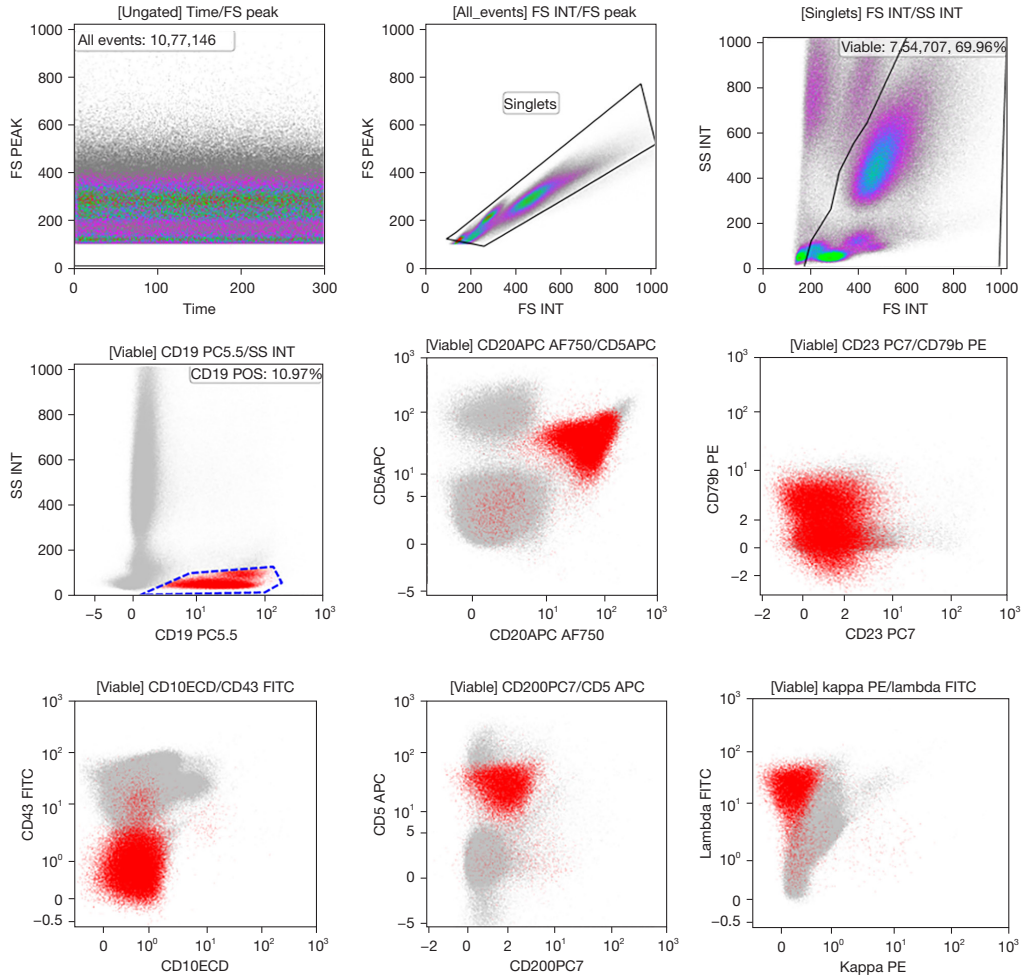

Figure 2 Flow cytometry of bone marrow aspirate: gated CD19 positive events (11% of viable cells) showing positivity for CD5, CD20, CD79b and surface lambda light chains. They are negative for CD10, CD23, CD20, CD43 and surface kappa light chains. This immunophenotype is consistent with mantle cell lymphoma. FS, forward scatter; SS, side scatter; INT, integration; POS, positive; PE, phycoerythrin; FITC, fluorescein isothiocyanate; APC, allophycocyanin.

(doxorubicin), oncovin (vincristine), prednisolone (R-CHOP)] resulted in normalization of renal function and resolution of proteinuria (4,5).

Paraneoplastic glomerulonephritis may be induced by cytokines secreted from tumor cells (12,13). The pathophysiology of paraneoplastic MCD has been studied in detail in Hodgkin lymphoma (14). Increased cytokine levels particularly IL-13, T-helper cell type2 related cytokines are thought to be responsible for the paraneoplastic inflammatory response in Hodgkin lymphoma associated MCD (15). However, primary mechanisms for other B-CLPD associated glomerulonephritis have not been well elucidated. B Cell receptor pathway modulation using targeted BTK inhibitors (BTKi's) are being increasingly used for managing B-CLPD's, particularly elderly and frail patients (16,17). In 2013, ibrutinib, a BTKi was first approved by FDA for the treatment of relapsed/refractory MCL (17). Apart from regulating B-cell function, BTK also has role in controlling cytokine production, phagocytosis and formation of inflammatory mediators by other cells of the immune system (18). Ibrutinib irreversibly inhibits BTK-homologous interleukin-2-inducible T-cell kinase, leading to downregulation of T_h2 cytokines (19). This particularly explains its role in steroid resistant/refractory chronic graft-versus-host-disease (20).

Recently several studies have suggested the role of Bruton

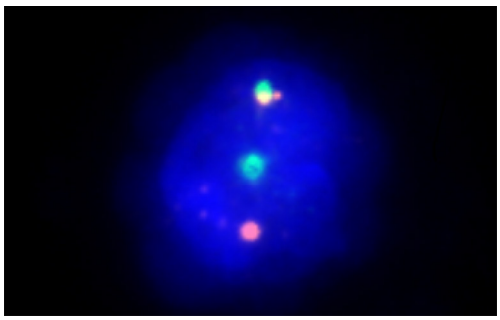

Figure 3 Fluorescent in-situ hybridization using dual color break apart probe showing CCND1 rearrangement (Metasystems GmBH; Germany).

tyrosine kinase pathway upregulation in the pathogenesis of lupus nephritis and IgA nephropathy (21-23). The safety of use of ibrutinib in the setting of lymphoma associated glomerulonephritis needs further studies. Potentially, ibrutinib can not only target the tumor per se, but also accelerate the recovery of glomerulonephritis through its broad spectrum Bruton tyrosine kinase inhibition. The safety of this drug in CLPD associated glomerulonephritis is not well reported, considering the rarity of this diagnosis. While ibrutinib is not excreted by the kidneys, its use has also been associated with worsening of renal function by causing interstitial nephritis, endothelial injury and

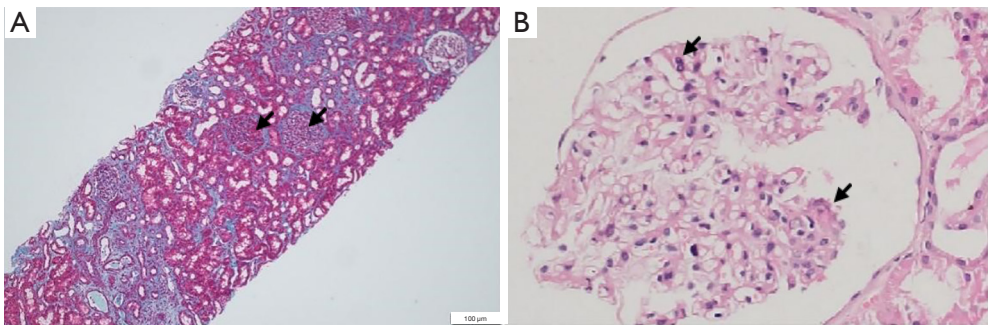

Figure 4 Left sided kidney core biopsy showing one glomerulus globally sclerosed, 1 glomerulus showing focal and segmental sclerosis in para hilar loop region [Masson's Trichome stain, magnification ×10 (A) and ×100 (B) respectively].

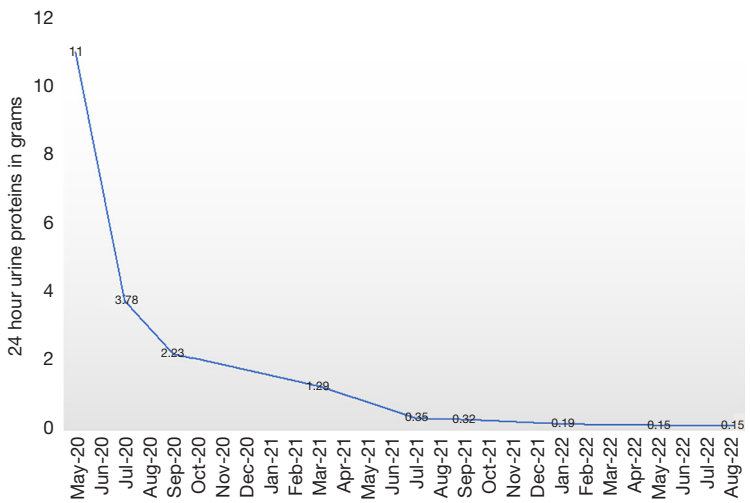

Figure 5 Graph showing the 24-hour urine protein (grams) at different time points after the initiation of ibrutinib in our case.

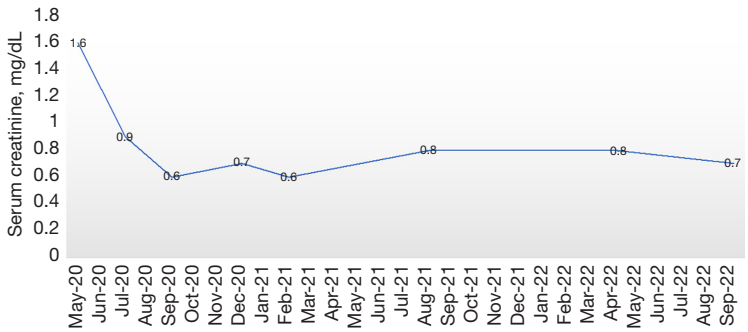

Figure 6 Graph showing the serum creatinine (mg/dL) at different time points after the initiation of ibrutinib in our case.

Table 1 Review of previously published cases of mantle cell lymphoma associated paraneoplastic glomerulonephritides

Case	Age (years)/sex	Type of kidney disease	Treatment	Renal outcome	Lymphoma outcome	Reference No.
1	68/M	Focal segmental glomerulonephritis	Short term hemodialysis, steroid, azathioprine, plasma exchange, CVP[!]	Normalisation of kidney function and proteinuria	Complete remission	(3)
2	67/M	Focal segmental glomerulosclerosis	Prednisolone, cyclosporine followed by R-CHOP[$] × 6 cycles	Improvement of proteinuria and renal function	Partial remission	(4)
3	77/M	Crescentic glomerulonephritis	Short term hemodialysis, CHOP* × 5 cycles, cytarabine × 2 cycles	Partial improvement in renal function and proteinuria	Died while on chemotherapy	(5)
4	68/M	Diffuse endocapillary proliferative glomerulonephritis	Hemodialysis, CHP[#] regimen	Normalisation of kidney function	Complete remission	(6)
5	59/–	Membranoproliferative glomerulonephritis, lymphoma infiltration	Short term hemodialysis, cyclophosphamide and steroid	Improvement of kidney function and proteinuria	Clinical response present (further details not available)	(7)
6	68/M	Membranoproliferative glomerulonephritis	Short term hemodialysis, rituximab, cyclophosphamide, dexamethasone × 3 cycles followed by H-CVAD[¶]	Renal function and proteinuria improved	Not available	(8)
7	55/F	Minimal change disease	Steroid × 10 weeks, CHOP* followed by autologous transplant	Normalisation of kidney function and proteinuria	Complete remission	(9)
8	77/M	Crescentic glomerulonephritis with lymphoma infiltration	Short-term hemodialysis, CVP[!] × 6 cycles	Partial improvement in renal function	Died of pulmonary haemorrhage after 3 months, further details not available	(10)
9	73/M	Focal segmental glomerulosclerosis	Ibrutinib 560 mg once daily	Normalisation of kidney function and proteinuria	Complete remission	Current case

[!], CVP: cyclophosphamide, vincristine, prednisolone; [$], R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), prednisolone; *, CHOP: cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), prednisolone; [#], CHP: cyclophosphamide, hydroxydaunorubicin (doxorubicin), prednisolone; [¶], H-CVAD: hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone. M, male; F, female.

worsening of hypertension (24,25). However, significant improvement in proteinuria, renal function, and remission of MCL in the current case with the use of ibrutinib suggests its potential safety as well as efficacy in MCL associated paraneoplastic glomerulonephritis (GN).

Conclusions

Our case illustrates an atypical presentation of MCL with nephrotic syndrome due to paraneoplastic FSGS. This case also highlights the potential role of upfront ibrutinib, a Bruton tyrosine kinase inhibitor, in inducing complete remission in MCL and paraneoplastic FSGS, especially in patients unfit for chemotherapy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://aol.amegroups.com/article/view/10.21037/aol-22-21/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aol.amegroups.com/article/view/10.21037/aol-22-21/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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