How we manage multiple myeloma with clonal hematopoiesis of indeterminate potential (CHIP): a case report

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is characterized by genetic alterations associated with hematologic neoplasms, posing clinical challenges in managing concurrent hematological malignancies. CHIP may complicate the treatment landscape due to its potential to influence disease progression and treatment response. We report a 73-year-old male with multiple myeloma (MM) harboring a CHIP PPM1D mutation, elucidating the complexities and therapeutic considerations in such cases.

Case Description: After four cycles of cyclophosphamide, bortezomib, and dexamethasone therapy, he achieved a partial response, followed by complete hematologic response (CR) post eight cycles of lenalidomide, dexamethasone, and bortezomib therapy. Despite this, upfront autologous hematopoietic stem cell transplantation (HSCT) was initially deemed unsuitable due to positive PPM1D CHIP status. HSCT proceeded after aggressive relapse with clonal evolution but yielded short-lived response. Following failure of >4 lines of therapy, he received chimeric antigen receptor T (CAR-T) cell therapy (ciltacabtagene autoleucel) for salvage. This approach successfully induced remission, which was maintained for 6 months.

Conclusions: This case report highlights MM management complexities in CHIP presence, suggesting potential utility of HSCT and CAR-T cell therapy. Prospective studies are necessary to evaluate the safety and efficacy of these therapies in myeloma patients with concurrent CHIP, aiming to optimize treatment strategies and improve outcomes in this challenging clinical context.

Keywords: Multiple myeloma (MM); case report; clonal hematopoiesis of indeterminate potential (CHIP); hematopoietic stem cell transplant

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Introduction

Hematopoietic stem cells (HSCs) exposed to DNA-damaging agents are prone to the accumulation of certain somatic mutations that may result in selective proliferation defined as clonal expansion (1). A subset of these proliferation-inducing somatic mutations occurs in genes that are associated with hematological malignancies such as multiple myeloma (MM) and have been termed clonal hematopoiesis of indeterminate potential (CHIP) (2,3). Presence of CHIP is associated with increased age, smoking, and exposure to prior radiation and cytotoxic chemotherapy, among other factors (4,5). Patients with CHIP have an increased risk of cardiovascular disease, chronic obstructive

pulmonary disease, and gout, among other conditions that may be affected by altered inflammation signaling pathways (6-8). There is limited data on the association between CHIP and the risk of cardiovascular disease specifically within patients with cancer since this population has high rates of CHIP that may be driven by the cancer itself, associated comorbidities, and/or cancer treatment exposures that may independently affect the risk. In one study, patients with MM undergoing HSCT with CHIP at baseline, the 5-year incidence of cardiovascular disease post-HCT was 21.1% and exceeded 30% in those who had both CHIP and a modifiable cardiovascular risk factor, significantly different from the comparable population without CHIP (9). Cardiovascular risk in CHIP continues to have other important, cumulative risk factors including age, dyslipidemia, and hypertension (10).

In a study on the Clinical Outcomes in MM to Personal Assessment of Genetic Profile (CoMMpass) cohort, CH was detected with a prevalence of approximately 10% of 986 in patients with newly diagnosed MM (11).

CHIP is also present in other plasma cell dyscrasias, although definite data regarding clinical significance remains elusive. A study by Gagnon *et al.* found clonal hematopoiesis at a prevalence of 21% in a cohort of plasma cell dyscrasias including MM, smoldering MM, monoclonal gammopathy of undetermined significance (MGUS) and others, without a significant difference between races (12). For instance, Tahri *et al.* found that progression from MGUS or smoldering Waldenström macroglobulinemia (WM), is associated with CHIP. Notably in this case, CHIP was not associated with inferior survival (13). Recent research has underscored the association between CHIP, particularly involving TP53 mutations, and the development of myeloid neoplasms following specific cancer treatments, such as rucaparib, suggesting a need for further exploration of its implications in therapeutic decisions (14).

In this case report, we highlight CHIP mutations and their increasing clinical relevance regarding the therapeutic decision making in a MM patient. We present this case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1945/rc).

Highlight box

Key findings

- The presence of PPM1D clonal hematopoiesis of indeterminate potential (CHIP) mutation poses significant challenges in the management of multiple myeloma (MM).
- The combination of high-dose melphalan followed by autologous hematopoietic stem cell transplantation (HSCT) and chimeric antigen receptor-modified T (CAR-T) cell therapy can be effective in achieving remission in MM patients with CHIP.
- Despite concerns about the risk of therapy-related myeloid neoplasms, individualized treatment strategies can lead to successful outcomes in such complex cases.

What is known and what is new?

- CHIP is associated with increased risks of hematologic malignancies and adverse outcomes in various cancer treatments.
- Managing MM in patients with CHIP mutations is particularly challenging due to potential therapy-related complications and the impact on treatment efficacy.
- This manuscript reports a detailed case of a 73-year-old male with MM and a PPM1D CHIP mutation, illustrating the therapeutic journey and clinical decision-making processes.
- It highlights the successful use of HSCT and CAR-T cell therapy, underscoring the potential for achieving remission in patients with high-risk CHIP mutations.

What is the implication, and what should change now?

- There is a critical need for prospective studies to explore the safety and effectiveness of HSCT and CAR-T cell therapy in MM patients with CHIP mutations.
- The findings advocate for the inclusion of CHIP status in the treatment planning and risk assessment for MM patients.
- Enhanced genetic testing and personalized treatment strategies should be considered to optimize outcomes for MM patients with CHIP.

Case presentation

A 73-year-old male with prior history of radiation therapy for prostate cancer presented to the emergency room with worsening lumbosacral back pain of 3 months duration. Evaluation revealed the presence of hypercalcemia, anemia, and acute renal failure. A magnetic resonance imaging (MRI) was performed and reported diffuse metastatic disease involving the lumbar spine, sacrum, and pelvis along with pathologic fractures of L2 and L4. A large lesion was noted at S2 and S3, resulting in the obliteration of the spinal canal at these levels and extension into the presacral space.

Bone marrow biopsy revealed a hypercellular marrow (92%) with clonal plasmacytosis of 82% by CD-138 staining. The malignant plasma cells were poorly differentiated with anaplastic features. The MM fluorescent in-situ hybridization (FISH) reported dup 1q and del 13q. Abnormal male karyotype was reported as follows: 82,XXYY,-1,add(1)(p13)x2,-2,add(3)(p13)x2,add(8)(q24)x2,-13,-13,-14,-14,-15,-16,add(20)(q11.2)x2,-22,-22,-22,-22,+3~8mar[cp2]/46,XY[5]. Chromosome analysis showed

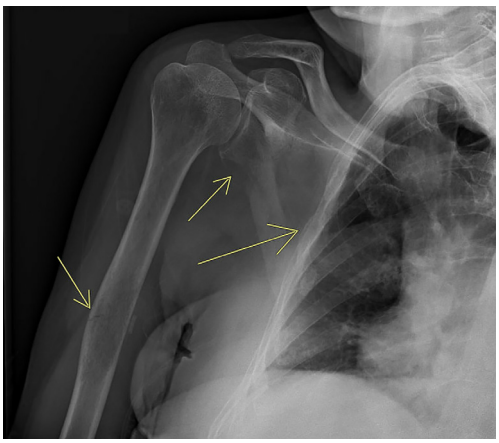

Figure 1 X-ray right shoulder and arm showed nondisplaced pathologic fracture of the mid right humerus with underlying 6 cm × 2 cm permeative lytic lesion. Additional 2 cm × 1 cm lytic lesion of the right scapula below the glenoid and chronic right anterior upper rib fractures with heterogeneous ossification (arrows).

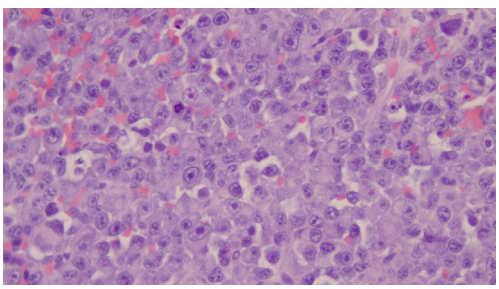

Figure 2 H&E ×40 of the humeral lesion: large markedly atypical plasma cells with high N:C ratios, macronucleoli and amphophilic cytoplasm. H&E, hematoxylin and eosin; N:C, nucleus-to-cytoplasm.

a male karyotype with one abnormal clone. The abnormal clone (2/7 cells) was near tetraploid and complex with structural and numerical changes including two copies of an unbalanced translocation of the short arm of chromosome 1 leading to 1p-, a loss of two copies of chromosome 13, and an unbalanced translocation of the long arm of chromosome 20 leading to 20q-. Near tetraploidy, del(1p), and loss of chromosome 13 are found in plasma cell myeloma. The del(20q) is reported in myeloid neoplasms. Additionally, the 54-gene myeloid next generation sequencing (NGS) panel performed on the bone marrow aspirate reported *PPM1D* E447 with variant allele frequency (VAF) of 12%. No morphologic evidence of bone marrow dysplasia noted.

The patient was diagnosed with revised international staging system (R-ISS) stage II IgG kappa MM and was started on bortezomib, dexamethasone and cylophosphamide (CyBorD) chemotherapy and achieved partial response after four cycles. The therapy was switched to lenalidomide, dexamethasone and bortezomib (VRD) and he achieved very good partial response (VGPR) after four cycles and complete hematologic response (CR) after eight cycles. A repeat bone marrow aspiration and biopsy reported to have normal morphology of the hematopoietic elements and without morphologic evidence of clonal plasma cells neoplasm, MM FISH markers came back normal, cytogenetics restored to normal male karyotype (46XY), but the NGS reported persistence of *PPM1D* E447 mutation. He was referred out for autologous hematopoietic stem cell transplantation (HSCT) for consolidation but due to the presence of *PPM1D* mutation and the presence of del(20q), he was deemed a high-risk candidate for myelodysplasia after high dose melphalan therapy and was not considered a candidate for HSCT. He continued VRD for 16 cycles and continued to maintain serologic CR until he presented with unbearable right arm pain. An X-ray showed non-displaced pathologic fracture of the mid right humerus with underlying 6 cm × 2 cm permeative lytic lesion. Additional 2 cm × 1 cm lytic lesion of the right scapula below the glenoid (*Figure 1*). A nuclear medicine positron emission tomography (PET) scan reported multiple new fluorodeoxyglucose (FDG) osseous lesions throughout the skeleton compatible with progression of disease. He underwent open reduction and internal fixation of right and the biopsy of the humeral lesion reported recurrent plasma cell neoplasm with plasmablastic features (*Figure 2*). FISH results from the bone lesion biopsy showed new mutation t(14:20) consistent with high risk MM with clonal evolution. A clinical impression of breakthrough progression of MM while on VRD therapy, without recurrence of M protein suggested plasmablastic disease versus light chain escape (non-secretory myeloma). At that time, we discontinued VRD therapy and began daratumumab, carfilzomib and dexamethasone (DKd). Fortunately, he achieved substantial radiologic response with six cycles of DKd therapy and the bone marrow biopsy at this point reported no clonal plasma cells or morphologic evidence of myelodysplastic syndrome (MDS), but the bone marrow aspirate remained positive for *PPM1D* E447 mutation. We requested that he be reevaluated for HSCT and successfully underwent melphalan (MEL) 200 HSCT after six cycles of DKd. He had no significant peri-HSCT transplant complication,

Table 1 Timeline of diagnosis and treatment phases in a case of MM with CHIP PPM1D mutation

Phase of disease	Treatment	Response
Diagnosis: MM with CHIP PPM1D	CyBorD	Partial response after 4 cycles
	VRD	VGPR after 4 cycles and CR after 8 cycles
	Patient not a candidate for HSCT due to the presence of PPM1D mutation and the presence of del(20q)	–
	Continued VRD for 16 cycles	Serologic CR
Progression: multiple new FDG osseous lesions	DKd for 6 cycles	Radiologic response
Continued remission	Melphalan HSCT	Complete radiologic response
		Day 100 bone marrow aspiration/biopsy: persistent PPM1D mutation
	Posttransplant maintenance therapy with daratumumab and carfilzomib	–
Extensive intramedullary progression of intense diffuse myeloma	Pomalidomide and dexamethasone	–
	CAR-T cell therapy: ciltacabtagene autoleucel	Radiologic complete response at 3-month post-CAR-T
Stable disease at 6-month post-CAR-T	Off therapy	–

MM, multiple myeloma; CHIP, clonal hematopoiesis of indeterminate potential; CyBorD, cyclophosphamide, bortezomib, dexamethasone; VRD, lenalidomide, dexamethasone, bortezomib; VGPR, very good partial response; CR, complete hematologic response; HSCT, hematopoietic stem cell transplantation; FDG, fluorodeoxyglucose; DKd, daratumumab, carfilzomib and dexamethasone; CAR-T, chimeric antigen receptor T.

and the engraftment was not delayed. A day 100 bone marrow aspiration/biopsy reported no morphologic evidence of clonal plasma cell neoplasm or myelodysplasia but showed persistent *PPM1D* E447 mutation. PET scan reported radiologic complete response. The patient started posttransplant maintenance therapy with daratumumab and carfilzomib but and is tolerating fine. A 6-month post-HSCT bone marrow aspiration/biopsy shows no clonal plasma cell neoplasm. He is tolerating therapy without significant myelosuppression. At one-year post-HSCT, he developed left sided arm pain and an MRI reported a large intramedullary lesion of the proximal humerus with lateral cortical breach and soft tissue extension which is at risk for pathologic fracture. Numerous sub-centimeter intramedullary lesions of the humeral diaphysis noted. A whole-body PET scan reported extensive intramedullary progression of intense diffuse myeloma. Patient initiated pomalidomide and dexamethasone and referred to chimeric antigen receptor T (CAR-T) cell therapy and received ciltacabtagene autoleucel and achieved radiologic complete response at 3-month post-CAR-T PET scan. Clinically he is stable and off therapy at 6-month post-CAR-T with persistent anemia and thrombocytopenia not needing transfusion. *Table 1* provides a comprehensive timeline outlining the key diagnostic and treatment phases in the clinical management of a patient.

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.

Discussion

CHIP and cancer therapy exposure

The driving factor for clonal hematopoiesis is the buildup of somatic mutations over the course of an individual's life. In fact, the whole genome of the HSC endures 14

mutations yearly, compared to just one mutation per decade for the exome. No matter the position, most of these mutations occur endogenously as a consequence of weakened DNA repair, altered telomerase activity, or sometimes both. Nevertheless, smoking, air pollutants, radiation exposure, and chemotherapy are examples of exogenous environmental mutagens that can induce these mutations. A history of chemotherapy and/or radiation is, in fact, the second most significant risk factor for CHIP after aging. Furthermore, genomic mutations have been linked to clonal selection pressures. Patients exposed to doxorubicin and platinum agents, for instance, have greater incidence of *PPM1D* mutations. Yet, this effect is not present after recovery from HSCT. Additionally, patients receiving taxanes, topoisomerase inhibitors, and radiation therapy have greater incidence of *PPM1D* mutations (15,16).

In our case, the patient's exposure to radiation therapy for his prostate cancer has most likely contributed to the presence of the *PPM1D* mutation detected by NGS. To provide yet another argument, a study by Bolton *et al.* found that *PPM1D* mutations were significantly overrepresented in ovarian and endometrial malignancies. The association with *PPM1D*, however, considerably diminished and resembled that of all other cancer types when patients without a prior history of cancer therapy were excluded. This suggests that the development of somatic mutations that cause clonal hematopoiesis depends on both the underlying malignancy and the cancer therapy (17).

CHIP detection: *NGS*

Although karyotyping, FISH, and polymerase chain reaction (PCR) are all performed to detect CHIP, NGS is the gold standard for its diagnosis because of its excellent sensitivity. NGS was performed on our patient using NeoTYPE™ Myeloid Disorders Profile of 54 gene panel that targets known mutations associated with acute myeloid leukemia (AML), myeloproliferative neoplasms (MPNs), MDS, chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML). Testing using this panel can aid in making therapy decisions, predicting prognosis, and can be used in clinical research. This is a generic and comprehensive profiling of myeloid neoplasms. This panel was chosen because the patient had macrocytic anemia at the time of presentation. The panel identified *PPM1D* E447 as the sole abnormality in this patient.

PPM1D gene mutation

In terms of our case, a few points are worth mentioning. The *PPM1D*, located on 17q23.2, encodes for a member of the protein phosphatase 2C family of serine/threonine protein phosphatases, which negatively regulate cellular responses to environmental stress, in part by inhibiting TP53 activity (4). Patients with therapy-related myelodysplastic syndrome are more likely to have *PPM1D* mutations than patients with primary myelodysplastic syndrome (15% versus 3%) and have poorer survival following HSCT (18). The *PPM1D* mutations can also be found in CHIP. In patients undergoing autologous stem cell transplantation for lymphoma, CHIP at the time of transplantation, particularly if *PPM1D* is mutated, is reportedly associated with inferior survival and increased risk of therapy-related myeloid neoplasm (TMN) in the form of AML and MDS (19).

CHIP is associated with poor outcomes in MM (prognosis)

Furthermore, people with MM who have CHIP have inferior clinical outcomes. For instance, Mouhieddine *et al.* found that patients with CHIP following HSCT had a greater rate of myeloma progression than those without CHIP. As a result, progression-free survival (PFS) and overall survival (OS) both declined. There could be numerous mechanisms at work when interpreting such data. Patients with CHIP may have experienced more chemotherapy-related side effects, such as cytopenia, leading to a delay in treatment or the use of suboptimal doses or frequency (20). Similarly, finding of CHIP mutation in a newly diagnosed myeloma may lead to a decision of not to provide the patient with HSCT due to perceived risk of myelodysplasia or myeloid neoplasm post-HSCT as was the initial decision in our patient. After the aggressive relapse, a decision to proceed with HSCT was made and the patient had an uneventful procedure. Despite advanced age and presence of *PPM1D* CHIP mutation, he tolerated the transplant well without delay in engraftment and there was no post-HSCT myelosuppression. Another relevant factor might be the alteration of the bone marrow's microenvironment brought on by proinflammatory cytokines, which might aid in the survival and development of myeloma. This discovery, however, was only made in myeloma patients who did not continue using the long-term immunomodulatory drug (IMiD), lenalidomide, after

HSCT. Regardless of whether CHIP was present or not, the group receiving lenalidomide maintenance experienced positive results (21). This observation is reinforced in another study showing that CHIP at time of MM diagnosis was not associated with inferior OS or PFS regardless of undergoing HSCT in a cohort of patients that all received IMiD-based therapies as maintenance. Moreover, CHIP at MM diagnosis was not associated with increased risk of developing a new hematologic malignancy or a new solid malignancy (11). Our patient was treated with lenalidomide for induction therapy and whether it impacted bone marrow microenvironment favorable for HSCT is unknown. Lenalidomide is a drug approved for MDS with deletion 5q and has been used also in low risk MDS without deletion 5q-drome (22).

Importance of distinguishing different mutations from one another

If we attempt to correlate CHIP mutations to patient outcomes, it is critical to distinguish between the various types of mutations. For instance, CHIP mutations in MM patients receiving HSCT were examined retrospectively in a study by Neri. CHIP mutations were associated with shorter PFS and OS in MM patients not receiving IMiD maintenance. Immunomodulator maintenance, nevertheless, was linked to enhanced PFS and OS regardless of CHIP status (23). The patients who received IMiD maintenance therapy post-HSCT had a longer median survival—8.5 years—compared to those not receiving IMiD maintenance—5.6 years. Similarly, among MM patients who did not receive IMiD maintenance, those with CHIP had a significantly shorter median survival of 3.6 versus 6.6 years in those without CHIP mutations. This may indicate IMiD such as lenalidomide's potential to ameliorate the negative prognostic factor associated with the presence of CHIP in MM patients undergoing HSCT. The study also revealed that the myeloma patients with CHIP who undergo HSCT were not at an elevated risk for myeloid malignancy that can develop years later after HSCT because of the therapies used to treat myeloma. This study's limitation is that it correlates clinical outcomes with all CHIP mutations at once. It would be interesting to focus on examining each mutation separately as they may interact differently with immunomodulators and affect patients with MM's clinical outcomes. This is particularly crucial from a therapeutic standpoint because a specific CHIP mutation can influence how MM patients are treated, including whether they receive chemotherapy, immunomodulators, or even HSCT.

Clinical significance of CHIP in MM

The most mutated genes in a single institution's large retrospective study (n=629) treated with HSCT following high dose melphalan conditioning were DNMT3A, TET2, TP53, ASXL1, and *PPM1D*. CHIP was present in 21.6% of cases. The existence of CHIP preceding HSCT for MM was not linked to an elevated risk of TMNs, unlike when recurrent non-Hodgkin lymphoma (NHL) was treated with HSCT. Despite this, the clinician's growing reluctance to recommend HSCT to MM patients who also have CHIP meant that our patient was not deemed a candidate for the procedure during initial evaluation but was later allowed to undergo HSCT after the aggressive relapse. What is the best maintenance plan for MM patients with CHIP after the HSCT? IMiD maintenance administration was substantially related with developing a future TMN in individuals who had CHIP in this study, despite improving PFS and OS for all patients regardless of CHIP status; 3.3% of individuals develop a TMN following a median of 2.7 years of IMiD maintenance (lenalidomide or thalidomide). Overall, the risk of TMN associated with IMiD maintenance is not increased by the existence of CHIP at the time of HSCT, and patients with CHIP who are treated with IMiD maintenance experience a survival advantage similar to that observed in patients with MM in general. Accordingly, we decided to advocate to move ahead with HSCT and post-HSCT maintenance therapy. He relapsed while on lenalidomide therefore we did not recommend IMiD maintenance post HSCT on this patient but decided to proceed with dual maintenance therapy with daratumumab and carfilzomib given high risk myeloma. MM patients with CHIP as of right now. Prospective long-term follow-up data on the effect of CHIP on survival and TMN are needed as the survival of MM patients keeps getting better, especially in the current period of widespread use of anti-CD38 monoclonal antibody treatments (daratumumab and isatuximab) for MM. Lenalidomide is currently being tested in clinical trials with or without daratumumab for post-HSCT maintenance therapy (AURIGA-NCT03901963 and S1803-NCT04071457), which could provide insight into how daratumumab affects CHIP and the eventual emergence of TMN.

Future outlook

Patients with MM and CHIP often have inferior outcomes

following autologous stem cell transplant, as the OS and PFS following transplant tends to be shorter than in patients without CHIP. The use of immunomodulatory therapy following HSCT is linked to longer disease response and better survival regardless of CHIP status. It is unknown if the apparent favorable effect of IMiD maintenance in this setting also applies to other post-HSCT antimyeloma maintenance therapy such as a proteasome inhibitor (PI) or anti-CD38 monoclonal antibody such as daratumumab is still unknown. Though development of a myeloid neoplasm post-HSCT in patients with MM and CHIP is a concern among clinicians, the available literature and our case report suggests that the HSCT is feasible and not a contraindication in this patient population. Post-HSCT maintenance therapy with IMiD and possibly a dual maintenance therapy may be indicated in high-risk patients. The utility of CAR-T cell therapy in myeloma patients with CHIP will probably evolve over time. In USA, currently, ciltacabtagene autoleucel is approved for relapsed or refractory MM who have received at least one prior line of therapy including a PI and an IMiD and who are refractory to lenalidomide (24). Due to earlier line of approval of ciltacabtagene autoleucel in MM, CAR-T cell therapy may be a safer consideration in myeloma patients with CHIP due to the risk of myelodysplasia from high dose melphalan conditioning.

Conclusions

Prospective studies are needed to further define the incidence, type and impact of CHIP on therapy and prognosis in patients with MM. Our case study demonstrates that both HSCT and CAR-T cell therapy are feasible if needed despite the presence of CHIP.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-23-1945/rc

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-23-1945/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1945/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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