

A rare dermatological manifestation of follicular spicules in a patient with multiple myeloma and end-stage renal disease on hemodialysis: A case report

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Received February 8, 2025; Accepted June 16, 2025

DOI: 10.3892/etm.2025.12930

Abstract. Multiple myeloma (MM) is a hematological malignancy characterized by the clonal expansion of malignant plasma cells within the bone marrow, leading to diverse systemic complications. While cutaneous manifestations of MM are uncommon, follicular spicules represent a highly specific but rare dermatological finding associated with MM. The present study presents the case of a 59-year-old man with MM who exhibited follicular acanthosis and hyperkeratosis as cutaneous indicators of the malignancy. The patient, with a history of stage 5 chronic kidney disease undergoing maintenance hemodialysis, was diagnosed with follicular spicules of MM (FSMM) through clinical evaluation and laboratory investigations. The present case highlights the clinical importance of recognizing rare cutaneous manifestations in MM, which can serve as critical diagnostic clues. Improved awareness of FSMM may facilitate a timely diagnosis and optimize

patient management, ultimately contributing to improved clinical outcomes in this challenging population.

Introduction

Multiple myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of plasma cells within the bone marrow, leading to disruption of normal hematopoiesis and immune regulation (1,2). This dysregulation results in a wide range of systemic complications, including anemia, immunosuppression, osteolytic lesions, hypercalcemia and renal dysfunction (3). Although MM primarily involves the bone marrow, extramedullary manifestations occur in ~4% of cases, with cutaneous involvement being exceptionally rare and affecting <1% of patients (4).

Cutaneous features of MM are diverse and often non-specific, including conditions such as light chain amyloidosis, cryoglobulinemia, xanthomatosis, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome, and sclerodermoid changes (5,6). Among these, follicular spicules of MM (FSMM) represent an uncommon but highly specific dermatological finding. Clinically, FSMM presents as fine, keratotic, spiny projections emerging from hair follicles, predominantly distributed over the nasal and facial regions (7). Histopathological examination typically reveals eosinophilic keratinous material within the follicles, frequently containing monoclonal immunoglobulin deposits that correspond to circulating paraproteins (8).

The precise pathogenesis of FSMM remains poorly defined (9). Recent studies have emphasized that abnormal deposition of monoclonal proteins within the follicular epithelium may contribute to the development of hyperkeratotic changes (10-12). Furthermore, a recent case report in patients with advanced chronic kidney disease (CKD) highlighted

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Key words: multiple myeloma, follicular spicules, dermatological manifestations, chronic kidney disease, end-stage renal disease, hemodialysis, hyperkeratosis, follicular acanthosis

the diagnostic challenge in distinguishing FSMM from other CKD-associated skin changes (12). Differential diagnoses include other hyperkeratotic conditions such as vitamin A deficiency, CKD-related dermatoses, HIV/acquired immunodeficiency syndrome and paraneoplastic syndromes; however, FSMM can be reliably distinguished through histological and immunofluorescence analysis demonstrating MM-specific monoclonal protein deposition (13).

The present report describes a clinically and histologically confirmed case of FSMM in a 59-year-old man with newly diagnosed MM and end-stage renal disease undergoing hemodialysis. The case details, including dermatological, hematological, as well as histopathological findings, underscore the diagnostic value of FSMM as an early cutaneous marker of MM. The present case contributes to the limited literature on FSMM, emphasizing the importance of dermatological vigilance and suggesting that prompt recognition of this rare phenotype may facilitate earlier diagnostic workup and improved patient management.

Case report

Patient information and clinical evaluation. The present report describes the case of a 59-year-old male patient diagnosed with MM and stage 5 CKD. Clinical data, including medical history, symptoms and physical examination findings, were collected at the time of hospital admission in February 2024 at The First Affiliated Hospital of Chongqing Medical and Pharmaceutical College (Chongqing, China). The patient underwent a comprehensive assessment involving hematological analysis, biochemical tests, karyotype analysis, immunofixation electrophoresis (IFE) and bone marrow biopsy. The serum vitamin A levels of the patient were within the normal range. Additionally, the patient tested negative for HIV via both serological and molecular methods.

Laboratory tests. Venous blood samples were collected in EDTA-containing tubes. The samples were allowed to clot at room temperature for 30 min and then centrifuged at 2,000 x g for 10 min at 4°C. The resulting supernatant (serum) was carefully extracted and used for biochemical and immunoassay analyses. Complete blood count was performed using an automated hematology analyzer (Beckman Coulter, Inc.). Serum calcium, creatinine, globulin, total protein and C-reactive protein (CRP) levels were measured using a biochemical analyzer (Roche Cobas 8000; Roche Diagnostics). Serum protein electrophoresis (SPE) and IFE were conducted using an agarose gel electrophoresis system (Sebia). Thyroid function tests, IL-6 and calcitonin levels were measured using electrochemiluminescence immunoassay kits (cat. no. 07027838 for IL-6 and cat. no. 05109342 for calcitonin; Roche Elecsys; Roche Diagnostics), and assays were performed on a Cobas e801 analyzer in accordance with the manufacturer's protocols. Serum ferritin and folate levels were determined using chemiluminescence immunoassay kits (cat. no. 7K61 for ferritin and cat. no. 8K41 for folate; Abbott Architect) as per the manufacturer's instructions. Serum albumin was measured using the same biochemical analyzer (Roche Cobas 8000; Roche Diagnostics) following the manufacturer's guidelines.

Karyotype analysis. Peripheral blood samples were collected in heparinized tubes and cultured in RPMI-1640 medium (Gibco; Thermo Fisher Scientific, Inc.) supplemented with 10% fetal bovine serum (Gibco; Thermo Fisher Scientific, Inc.) and 1% phytohemagglutinin-M (cat. no. L8754; Sigma-Aldrich; Merck KGaA) for 72 h at 37°C in a 5% CO₂ incubator. After incubation, colchicine (cat. no. C9754; Sigma-Aldrich; Merck KGaA) was added at a final concentration of 0.1 µg/ml and the cells were incubated for an additional 2 h at 37°C. Following colchicine treatment, lymphocytes were harvested by centrifugation (1,000 x g for 10 min) and hypotonic treatment using 0.075 M KCl for 20 min at 37°C. Cells were then fixed with freshly prepared in methanol:acetic acid (3:1) fixative at room temperature for 30 min (three changes). Metaphase chromosome spreads were prepared and subjected to G-banding using standard trypsin-Giemsa staining. Chromosomal abnormalities were analyzed under a light microscope (Olympus BX53; Olympus Corporation) and described in accordance with the International System for Human Cytogenomic Nomenclature (ISCN 2020) (14).

SPE and IFE. SPE was performed using a semi-automated agarose gel electrophoresis system (Hydrasys 2 Scan; Sebia) according to the manufacturer's protocol, to detect the presence of monoclonal M-spike bands in the γ region. IFE was conducted using antisera specific for IgG, IgA, IgM, and κ and λ light chains (Hydrigel IF kit; cat. no. 4460; Sebia) following the manufacturer's instructions. After electrophoresis and fixation, the gels were stained and imaged using a gel documentation and analysis system (Bio-Rad Gel Doc XR+; Bio-Rad Laboratories, Inc.).

Bone marrow biopsy and histopathological examination. A bone marrow biopsy was performed under local anesthesia using 2% lidocaine hydrochloride (5 ml; Hubei Tianyao Pharmaceutical Co., Ltd.). The procedure was conducted using an 11-gauge Jamshidi needle (Cardinal Health Canada, Inc.). The biopsy specimen was immediately fixed in 10% neutral buffered formalin (Wuhan Servicebio Technology Co., Ltd.) at room temperature (20–25°C) for 24 h, followed by decalcification in 10% EDTA solution (Wuhan Servicebio Technology Co., Ltd.) for 48 h. Samples were dehydrated, embedded in paraffin and sectioned into 4-µm slices using a microtome. The sections were rehydrated in descending alcohol series (100, 95, 85 and 75% ethanol) and rinsed with PBS (pH 7.4). Hematoxylin and eosin (H&E) staining was performed using Mayer's hematoxylin (Wuhan Servicebio Technology Co., Ltd.) for 5 min at room temperature, followed by eosin (1%) staining for 2 min at room temperature (20–25°C). Slides were washed and mounted for microscopic observation under a light microscope (BX53, Olympus Corporation).

For immunohistochemical (IHC) analysis, paraffin-embedded sections underwent antigen retrieval in citrate buffer (pH 6.0; Wuhan Servicebio Technology Co., Ltd.) at 95°C for 20 min using a water bath. After cooling and washing with PBS, endogenous peroxidase activity was blocked using 3% hydrogen peroxide for 10 min at room temperature. Non-specific binding was blocked with 5% normal goat serum (Wuhan Servicebio Technology Co., Ltd.) for 20 min at room temperature. No permeabilization step was applied,

as all antibodies targeted surface or membrane-associated antigens. Primary antibodies were incubated overnight at 4°C, including: CD138 (cat. no. ab34164; dilution 1:100; Abcam), CD56 (cat. no. ab75813; dilution 1:200; Abcam), κ light chain (cat. no. ZM-0317; dilution 1:150; OriGene Technologies, Inc.) and λ light chain (cat. no. ZM-0318; dilution 1:150; OriGene Technologies, Inc.). After cooling, sections were washed with phosphate-buffered saline (PBS, pH 7.4). After washing, HRP-conjugated secondary antibodies (goat anti-rabbit/mouse IgG; cat. no. PV-6000; dilution 1:200; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) were applied for 30 min at room temperature. Visualization was achieved using 3,3'-diaminobenzidine (cat. no. ZLI-9018; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) as the chromogenic substrate, followed by counterstaining with hematoxylin. Slides were observed under a light microscope (Olympus BX53; Olympus Corporation). Appropriate positive and negative controls were included for each staining run. IHC procedures were performed using the automated BenchMark ULTRA staining system (Roche Diagnostics GmbH) according to manufacturer protocols where applicable.

Findings

Basic information. The patient was a 59-year-old man with a medical history significant for stage 5 CKD, who was receiving maintenance hemodialysis. The patient presented in February 2024 with complaints of generalized weakness persisting for 2 days. Over the previous month, the patient had been hospitalized in the Department of Gastroenterology of the First Affiliated Hospital of Chongqing Medical and Pharmaceutical College for symptoms including cough, sputum production and melena. Laboratory findings during that hospitalization revealed impaired renal function and anemia, ultimately leading to the diagnosis of stage 5 CKD. The patient had been undergoing regular hemodialysis three times per week, with hemoglobin levels consistently maintained at ~60 g/l (normal range, 120-160 g/l), indicating persistent moderate-to-severe anemia.

Clinical observations included notable anemia, hyperphosphatemia, hypocalcemia and general malaise. Additionally, the patient experienced an intermittent cough with hemoptysis, melena of unspecified quantity and progressive abdominal distension. Despite these symptoms, urination remained normal, and the patient had a significant unintentional weight loss of ~9 kg. Prior to the onset of these symptoms, the patient had been generally healthy, and had no history of hypertension, coronary artery disease or diabetes mellitus.

At the time of admission in February 2024, the patient reported a prior diagnosis of hypothyroidism and had been taking levothyroxine sodium at a dose of 50 μ g per day for the past 2 months. They had no known history of dysentery, malaria, viral hepatitis, tuberculosis or other infectious diseases, nor any known exposure to hepatitis or tuberculosis. The patient denied any history of trauma, blood transfusions, drug allergies or food allergies.

Physical examination. On presentation, the patient was alert and oriented, with a dusky complexion. Dermatological examination revealed numerous dense, pinpoint, brown keratotic papules on the facial skin, consistent with the cutaneous manifestations of MM.

The vital signs of the patient were as follows: Body temperature, 36.4°C (normal, 36.1-37.2°C); pulse rate, 106 beats per min (normal, 60-100 bpm); respiratory rate, 20 breaths per min (normal, 12-20 breaths per min); and blood pressure, 115/78 mmHg (normal, 90/60-120/80 mmHg). Respiratory system findings included the following: Auscultation revealed slightly coarse breath sounds bilaterally, with no evidence of dry or wet rales. Cardiovascular system findings included the following: The heart rate was regular, and no murmurs were detected in any of the cardiac valve regions. In addition, the abdomen was flat, with periumbilical pigmentation; it was soft, non-tender and exhibited no rebound tenderness or muscle rigidity. Murphy's sign was negative and no mobile turbidity was detected. In addition, bowel sounds were normal. In the lower extremities, no edema was observed in either lower limb. Additional findings included a 3-cm surgical scar on the left wrist. A palpable tremor (thrill) was identified at the site of a previously constructed arteriovenous fistula (AVF) for hemodialysis, located on the left forearm. A continuous vascular murmur (bruit) was also audible upon auscultation, consistent with a functioning AVF.

Inspection results. The physical examination indicators of the patient are shown in Table I. Regarding the hematological analysis, the patient exhibited anemia with a reduced red blood cell count ($1.54 \times 10^{12}/l$), hemoglobin level (46 g/l) and blood platelet count ($75 \times 10^9/l$), which were all below the reference ranges. The white blood cell count was within normal limits. CRP levels were elevated at 13.09 mg/l (reference value, ≤ 10 mg/l) suggesting an inflammatory state. Notably high levels of calcitonin (3.77 ng/ml; reference value, < 0.15 ng/ml) and IL-6 (6,124.5 pg/ml; reference value, < 6.6 pg/ml) were detected, indicating an immune and inflammatory response associated with the disease. The liver and kidney function test results were as follows: Serum calcium was elevated at 2.96 mmol/l (reference value, 2.25-2.75 mmol/l) and creatinine was markedly raised (566.53 μ mol/l; reference value, 53-106 μ mol/l), indicating renal impairment. Protein markers, such as globulin (64.73 g/l; reference value, 20-40 g/l) and total protein (102.86 g/l; reference value, 63-82 g/l), were also elevated.

SPE results indicated that the M protein percentage was 36.7%, characteristic of monoclonal gammopathy. Other immunoglobulin abnormalities included elevated IgA (12.2 g/l; reference value, 0.71-3.35 g/l) and an increased λ light chain (52.0 g/l; reference value, 3.13-7.23 g/l), further indicating a monoclonal protein spike. Furthermore, the patient had a high level of hepatitis B virus surface antibody (909.71 mIU/ml; reference value, 0-10 mIU/ml), with normal levels for other hepatitis markers. Thyroid function tests demonstrated a reduced triiodothyronine level (0.93 nmol/l; below the normal range), whereas thyrotropin (0.59 mIU/l) was within the reference range. The results of the anemia test revealed that ferritin levels were high ($> 3,000$ ng/ml; reference value, 25-350 ng/ml), suggesting chronic disease-related anemia, whereas folate levels were low (3.03 ng/ml; reference value, 5.21-20 ng/ml), which could contribute to anemia. These results indicated a comprehensive systemic involvement in the patient, which supported the diagnosis and informed the clinical management of MM with associated complications, including anemia, renal insufficiency and immune dysregulation.

Table I. Physical examination indicators of the patient.

Variable	Inspection results	Reference value
Hematological analysis		
White blood cell count, $\times 10^9/l$	4.63	3.50-9.50
Red blood cell count, $\times 10^{12}/l$	1.54	4.0-5.50
Hemoglobin, g/l	46.00	120-160
Blood platelet count, $\times 10^9/l$	75.00	100-300
C-reactive protein, mg/l	13.09	≤ 10.0
Calcitonin, ng/ml	3.77	< 0.15
IL-6, pg/ml	6,124.50	< 6.60
Liver and kidney function analysis		
Serum calcium, mmol/l	2.96	2.25-2.75
Creatinine, $\mu\text{mol/l}$	566.53	53-106
Globulin, g/l	64.73	20-40
Total protein, g/l	102.86	63-82
Serum protein electrophoresis results		
Albumin, g/l	46.00	35-55
$\alpha 1$ globulin, g/l	3.10	0.01-0.03
M protein, %	36.70	-
Globulin, g/l	49.53	20-40
Serum κ light chain, g/l	3.87	6.29-13.50
Serum λ light chain, g/l	52.00	3.13-7.23
Immunoglobulin A, g/l	12.2	0.80-4.53
Immunoglobulin G, g/l	4.87	7.51-15.60
Immunoglobulin M, g/l	0.14	0.46-3.04
Hepatitis B virus surface antibody, mIU/ml	909.71	0-10
Hepatitis B virus core antibody, IU/ml	0.62	< 0.35
Hepatitis B Virus e antibody, IU/ml	< 0.100	< 0.15
Hepatitis B virus e antigen, IU/ml	< 0.050	< 0.10
Thyroid function tests		
Triiodothyronine, nmol/l	0.93	1.6-3.0
Thyrotropin, mIU/l	0.59	0.4-5.0
Anemia tests		
Ferritin, ng/ml	$> 3,000$	25-350
Folate, ng/ml	3.03	5.21-20

Karyotype analysis results. The karyotype analysis of the patient revealed extensive chromosomal abnormalities consistent with MM and indicative of notable genetic instability. The ISCN results were as follows: ‘83-85<4n>,XXY,-Y,+1,+1,dic(1;10)(p13;q26),psu idic(1)(p21),add(7)(q32),add(8)(p23)x2,?add(17)(q22)x2,-19,-19,-20,-21,-21,-22,+1-2mar,inc[cp4]/46,XY[16]’.

The key findings in the present study included: i) Hyperdiploidy with tetraploid cells (83-85 chromosomes), the presence of tetraploid cells (83-85 chromosomes) indicates hyperdiploidy, which is often associated with advanced disease. ii) extra X chromosome (XXY), the additional X chromosome is an unusual finding and may reflect somatic changes linked to malignancy. iii) loss of Y chromosome (-Y), the absence of the Y chromosome is frequently observed in hematological malignancies and is considered a marker of disease progression in MM. iv) polysomy of chromosome 1 (+1,+1), the addition of

two extra copies of chromosome 1 suggests high-level polysomy, which is commonly associated with aggressive forms of myeloma and may indicate a poorer prognosis. v) dicentric chromosome [dic(1;10)(p13;q26)], the presence of a dicentric chromosome formed by the fusion of chromosomes 1 and 10 suggests structural chromosomal instability, which can serve a role in tumorigenesis. vi) pseudo-isodicentric chromosome [psu idic(1)(p21)], this abnormality in chromosome 1, featuring duplication and inversion, reflects further chromosomal rearrangement, indicative of genomic instability. vii) additional material on chromosomes 7, 8, and 17: Specifically noted in the ISCN as add(7)(q32), add(8)(p23)x2, and ?add(17)(q22)x2, the term ‘add’ indicates the presence of unidentified extra chromosomal material at these loci. These changes may represent gene amplifications or rearrangements involved in disease progression. viii) losses of chromosomes 19, 20, 21 and 22 (-19,-20,-21,-22), the deletion of these chromosomes further



Figure 1. Karyotype analysis revealing complex chromosomal abnormalities in advanced MM. Conventional karyotyping revealed multiple numerical and structural abnormalities (red arrows) characteristic of high-risk MM: i) Hyperdiploidy with tetraploid cells ($83-85<4n>,XXY$), including an additional X chromosome. ii) Loss of Y chromosome (-Y), a common finding in hematological malignancies. iii) High-level polysomy of chromosome 1 (+1,+1), totaling four copies, indicating aggressive disease. iv) Dicentric chromosome [dic(1;10)(p13;q26)], suggesting genomic instability. v) Pseudo-isodicentric chromosome [psu idic(1)(p21)], reflecting complex chromosomal rearrangement. vi) Additional material on chromosomes 7 and 8 [add(7)(q32),add(8)(p23)x2]. vii) Possible unidentified material on chromosome 17 [?add(17)(q22)x2]. ix) Monosomy of chromosomes 19, 20, 21 and 22 (green arrows). xi) One to two marker chromosomes (+1-2mar). xii) Mosaic karyotype: Four abnormal clones with complex karyotype and 16 normal male karyotypes (46,XY), consistent with clonal evolution. MM, multiple myeloma.

supports the presence of extensive genomic instability, often seen in advanced stages of MM. ix) marker chromosomes (mar), the presence of 1-2 marker chromosomes signifies structurally abnormal, unidentifiable chromosomes, which are frequently observed in hematological malignancies and represent complex karyotypic alterations. x) mosaicism (inc[cp4]/46,XY[16]), the karyotype exhibits mosaicism, with four abnormal cell clones (cp4) and 16 cells with a normal male karyotype (46,XY). This mosaic pattern suggests clonal evolution within the disease (Fig. 1).

In summary, these findings collectively indicated a high degree of chromosomal complexity and genetic instability, typical of advanced MM (12). The chromosomal abnormalities, including polysomy, structural rearrangements, marker chromosomes and loss of specific chromosomes, are associated with disease progression and a poor prognosis.

IFE analysis results. SPE revealed a prominent M-spike in the γ region, consistent with the presence of monoclonal protein (Fig. 2A). IFE demonstrated specific staining for IgA

and λ light chains, confirming a monoclonal IgA λ component (Fig. 2B). A second IFE analysis was performed on a follow-up serum sample, which consistently showed the same IgA λ monoclonal pattern (Fig. 2C). This repeat testing served as a confirmatory step to exclude false positivity and to strengthen diagnostic reliability. These findings provided crucial diagnostic evidence for the presence of monoclonal gammopathy, a hallmark feature of MM.

Bone marrow biopsy results. Bone marrow biopsy revealed markedly active hematopoietic tissue proliferation, occupying >90% of the marrow volume, with a corresponding reduction in adipose tissue. Plasma cell hyperplasia was evident, characterized by medium-sized cytoplasm, abundant cytosol, nuclear eccentricity and patchy distribution. Additionally, areas of fibrous tissue proliferation were observed, as shown by representative hematoxylin and eosin-stained sections of the bone marrow biopsy.

The IHC findings are summarized in Table II, and provide critical insights into the cellular and molecular characteristics of the bone marrow biopsy. Weak positive

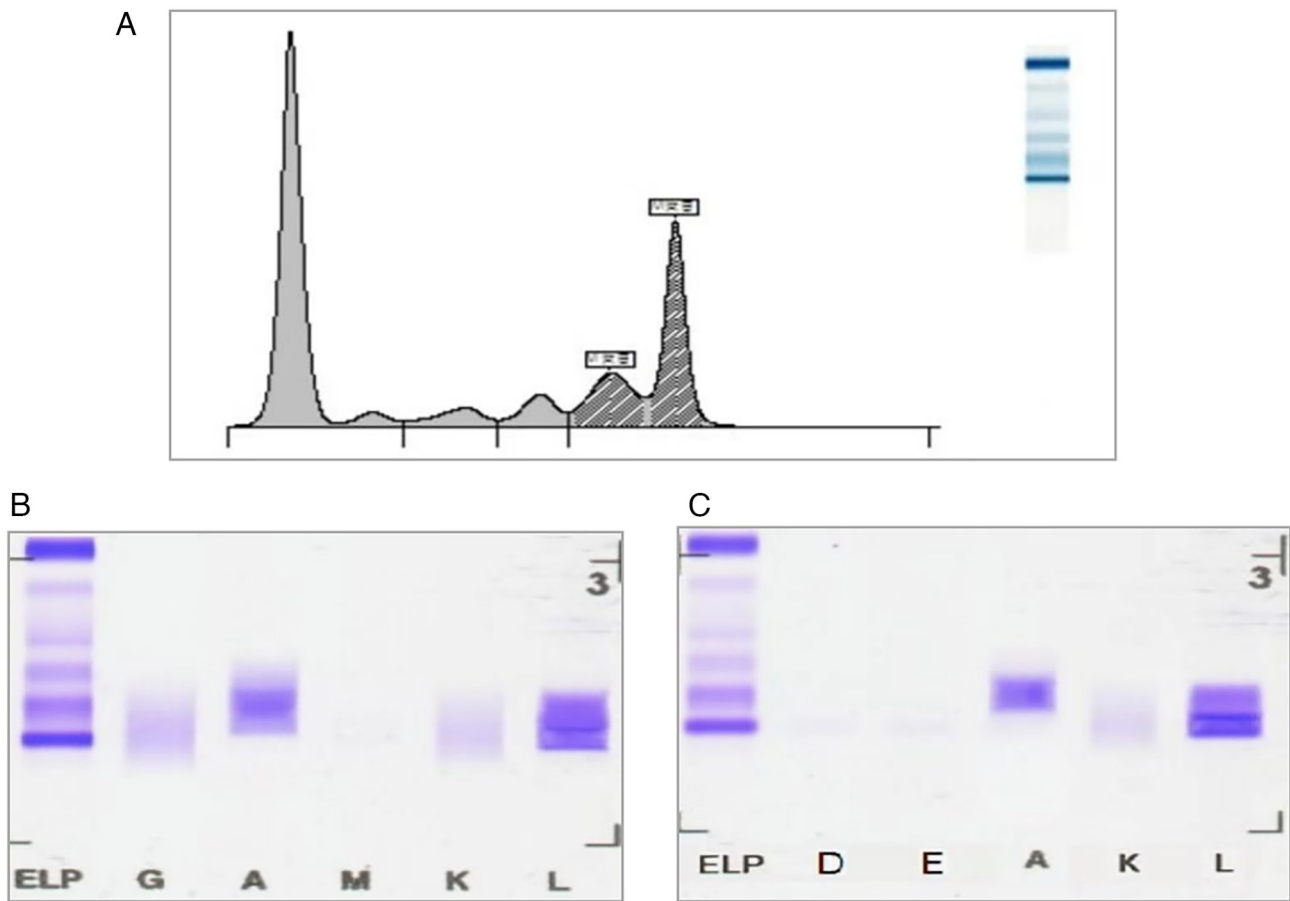


Figure 2. SPE and immunofixation confirming monoclonal gammopathy. (A) SPE demonstrating an M-spike in the γ region. (B) Immunofixation electrophoresis revealing a monoclonal IgA λ pattern, confirming the presence of IgA- λ type multiple myeloma. (C) Immunofixation electrophoresis further confirming the monoclonal IgA λ pattern. AU, arbitrary units; SPE, serum protein electrophoresis. ELP, electrophoresis reference; G, IgG; A, IgA; M, IgM; K, κ light chain; L, λ light chain; D, IgD; E, IgE.

staining was observed for both CD3 and CD20, indicating limited involvement of T cells (CD3) and B cells (CD20). For CD56, patchy positive staining was noted. For CD56, patchy and heterogeneous positive staining was noted across the biopsy sample. CD56, a neural cell adhesion molecule, is frequently expressed in plasma cell dyscrasias, including MM (15). The non-uniform distribution and limited number of CD56-positive cells suggested partial expression in this case. For CD138, patchy positive staining was also present, confirming the presence of plasma cells. Regarding κ and λ light chains, κ light chain staining was negative, whereas λ light chains exhibited fragmented positive staining. This pattern indicates a monoclonal plasma cell population with λ light chain restriction, consistent with the diagnosis of MM. For multiple myeloma oncogene 1 (MUM-1), fragmented positive staining was detected, characteristic of late-stage B-cell differentiation and plasma cells, a hallmark feature in MM cases. The immunohistochemical profile, including the expression of CD138, CD56, MUM-1 and the λ light chain restriction, strongly supported the diagnosis of MM with a monoclonal λ light chain profile (16).

The bone marrow biopsy findings demonstrated notable proliferation of monoclonal plasma cells, accounting for ~70% of the marrow composition. These results are consistent with a diagnosis of plasma cell myeloma (PCM) (17).

Histopathological and immunohistochemical findings.

A skin punch biopsy was obtained from the facial keratotic papules to characterize the follicular spicules. H&E staining revealed marked follicular plugging with compact orthokeratosis and keratinous debris occupying dilated follicular infundibula. The surrounding dermis exhibited mild perivascular lymphocytic infiltration without evidence of epidermal atypia. Congo red staining, performed on both skin and bone marrow specimens, revealed eosinophilic amorphous deposits in the dermis and marrow. Under polarized light, these deposits exhibited classic apple-green birefringence, confirming amyloid deposition (Fig. 3A).

To further evaluate the bone marrow biopsy, IHC staining was conducted to identify cellular components and assess clonality of infiltrating plasma cells. Scattered CD3-positive T cells and CD20-positive B cells were detected, indicating minimal lymphoid infiltration (Fig. 3B and C). CD56 staining showed diffuse membranous positivity (Fig. 3D), suggesting aberrant expression in neoplastic plasma cells or natural killer (NK) cell involvement. CD138 was diffusely and strongly expressed on infiltrating plasma cells (Fig. 3E), confirming their plasma cell phenotype. Light chain restriction analysis showed complete absence of κ light chain expression (Fig. 3F) and intense diffuse positivity for λ light chains (Fig. 3G), indicating monoclonal λ light chain restriction. MUM-1 staining demonstrated

Table II. Immunohistochemistry findings for the patient.

Variable	Result
CD3	Weakly positive staining
CD20	Weakly positive staining
CD56	Patchy positive staining
CD138	Patchy positive staining
κ light chain	Negative staining
λ light chain	Fragmented positive staining
Multiple myeloma oncogene 1	Fragmented positive staining

diffuse nuclear positivity in plasma cells (Fig. 3H), supporting their plasmacytic differentiation. Additionally, H&E staining of the bone marrow revealed diffuse infiltration by atypical plasma cells with irregular nuclear morphology (Fig. 3I), consistent with plasma cell myeloma (PCM). Positive staining for amyloid deposits in bone marrow biopsy further confirmed amyloid deposition, with strong eosinophilic characteristics and brown staining (Fig. 3J).

Together, the histopathological and immunophenotypic findings from the cutaneous tissue and bone marrow biopsy confirmed the diagnosis of systemic amyloid light-chain amyloidosis secondary to monoclonal PCM, presenting with rare cutaneous involvement in the form of follicular spicules (18).

Flow cytometric immunophenotyping for hematologic tumor classification. Multiparameter flow cytometry was performed on fresh bone marrow aspirate samples collected in EDTA-containing tubes to characterize the immunophenotypic profiles of hematopoietic cell populations. Sample acquisition was conducted on a BD FACSCanto™ II flow cytometer (BD Biosciences). Data analysis was performed using FlowJo™ software, version 10.8.1 (BD Biosciences). Gating strategies were applied to total nucleated cells (NCs) using CD45 and side scatter profiles. As shown in Fig. 4A, lymphocytes accounted for 27.76% of total NCs. The CD4/CD8 ratio was decreased, indicating a shift in T-cell subset balance, which may reflect immune dysregulation associated with plasma cell disorders. CD57⁺ large granular lymphocytes (LGLs) were detected within the normal reference range (2-15% of total lymphocytes) (Fig. 4B and C), suggesting no evidence of LGL expansion or chronic LGL leukemia. CD19⁺ B lymphocytes constituted 13.08% of the lymphocyte population, with normal distributions of precursor and mature subsets, indicating no disruption in B-cell maturation. Notably, a substantial expansion of plasma cells was observed (Fig. 4D). As shown in Fig. 4E, gating on CD38 and CD45 expression revealed a distinct CD38^{bright+} (CD38^{bri+}) population, accounting for 33.19% of total NCs. These cells exhibited low CD45 expression and high CD38 expression, a typical immunophenotypic hallmark of malignant plasma cells. The markedly increased proportion of CD38^{bri+} cells indicated significant plasma cell infiltration within the bone marrow.

Further immunophenotypic analysis of the CD38^{bri+} gated population was conducted to assess light chain restriction. As

demonstrated in Fig. 4F, intracellular staining for cytoplasmic immunoglobulin light chains revealed predominant expression of λ light chains in 97.37% of the gated plasma cells, with minimal κ expression (0.03%). This pronounced λ light chain restriction confirms the presence of a clonal plasma cell population and supports the diagnosis of PCM. Collectively, these flow cytometry findings demonstrated substantial clonal proliferation of λ-restricted malignant plasma cells within the bone marrow, consistent with a diagnosis of MM.

Imaging and histopathological findings. A thorough imaging evaluation was conducted, including CT scans of the pelvis, cervical spine and head. The key findings are summarized as follows: i) Cranial findings, head CT revealed no abnormalities in the brain parenchyma. Sinus findings revealed evidence of bilateral maxillary and ethmoid sinusitis. ii) Skeletal lesions, multiple hypodense lesions were identified in the skull, several vertebrae, bilateral ribs, scapulae and pelvic bones, which are findings consistent with lytic lesions of MM. iii) Fractures and spinal changes, bilateral pathological rib fractures, compression of the T12 vertebral body and a suspected intravertebral lesion in T1 were observed, along with degenerative changes in the spine. iv) Pulmonary findings, bilateral lung infections, pleural thickening and small bilateral pleural effusions were evident (Fig. 5A-C). v) Renal findings, CT revealed small calculi in the right kidney. vi) Abdominal findings, increased soft tissue density surrounding the abdominal aorta was detected. vii) Pelvic findings, small pelvic effusions were observed. viii) Histopathological findings, dermatopathological analysis revealed squamous epithelium with areas of hyperkeratosis (Fig. 5D). Furthermore, Fig. 6 presents a detailed histopathological view, showing an area of extensive infiltration of malignant plasma cells in the dermal layer, consistent with cutaneous involvement in MM. These findings collectively indicated advanced MM with extensive skeletal involvement and associated systemic complications.

Treatment timeline and clinical course

Diagnosis. The patient was diagnosed with MM, stage III, subtype B, IgA-λ type in February 2024. Concomitantly, the patient had stage 5 CKD, for which maintenance hemodialysis (three sessions per week) was initiated as supportive therapy.

Disease progression and therapeutic interventions. The clinical course and major therapeutic milestones are summarized in Fig. 7. The condition of the patient exhibited episodic deterioration with corresponding escalation in supportive care. Notably, data from March 2024 revealed critical insights into disease progression.

i) 12 days post-admission: The patient was prescribed a supportive pharmacological regimen, which included the following treatments: i) Levothyroxine sodium (50 μg, oral, daily) to treat hypothyroidism, which was diagnosed based on thyroid function tests; ii) esomeprazole (40 mg, oral, daily), prescribed for gastroesophageal reflux disease and to prevent gastric ulcers, a common side effect of other medications used in the patient's treatment.; iii) urotoxin (5 ml, topical, applied twice daily) to treat localized urinary tract infection symptoms, primarily urinary discomfort; iv) Nadex cream (1% strength, topical, applied twice daily), applied to manage dermatological symptoms related to skin irritation and hyperkeratosis associated with the patient's condition; v) urea preparations (10%,

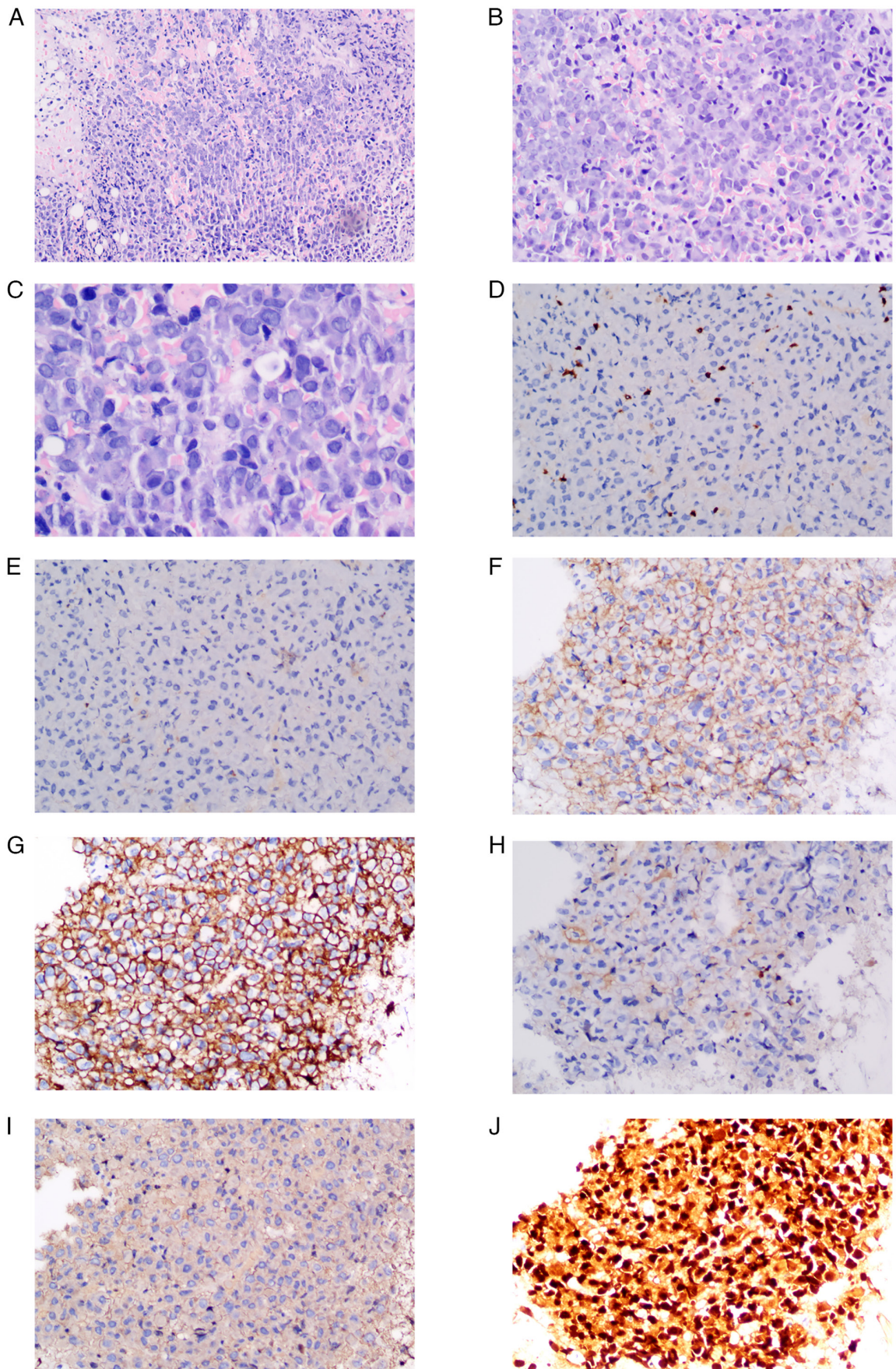


Figure 3. Immunohistochemical characterization of bone marrow biopsy. (A) Congo red staining showed amyloid deposits with birefringence under polarized light, confirming amyloidosis. (B) Scattered CD3⁺ T cells. (C) CD20⁺ B cells. (D) Diffuse CD56 positivity indicating natural killer cell involvement. (E) Diffuse CD138 staining marking plasma cell infiltration. (F) Negative κ light chain staining. (G) Diffuse positive staining of λ light chains, confirming monoclonality. (H) Multiple myeloma oncogene 1-positivity indicated plasma cell differentiation. (I) Hematoxylin and eosin staining revealed diffuse infiltration by atypical lymphoid/plasma cells. (J) Positive staining for amyloid deposits in bone marrow biopsy. All images were captured under a light microscope at x400 magnification.

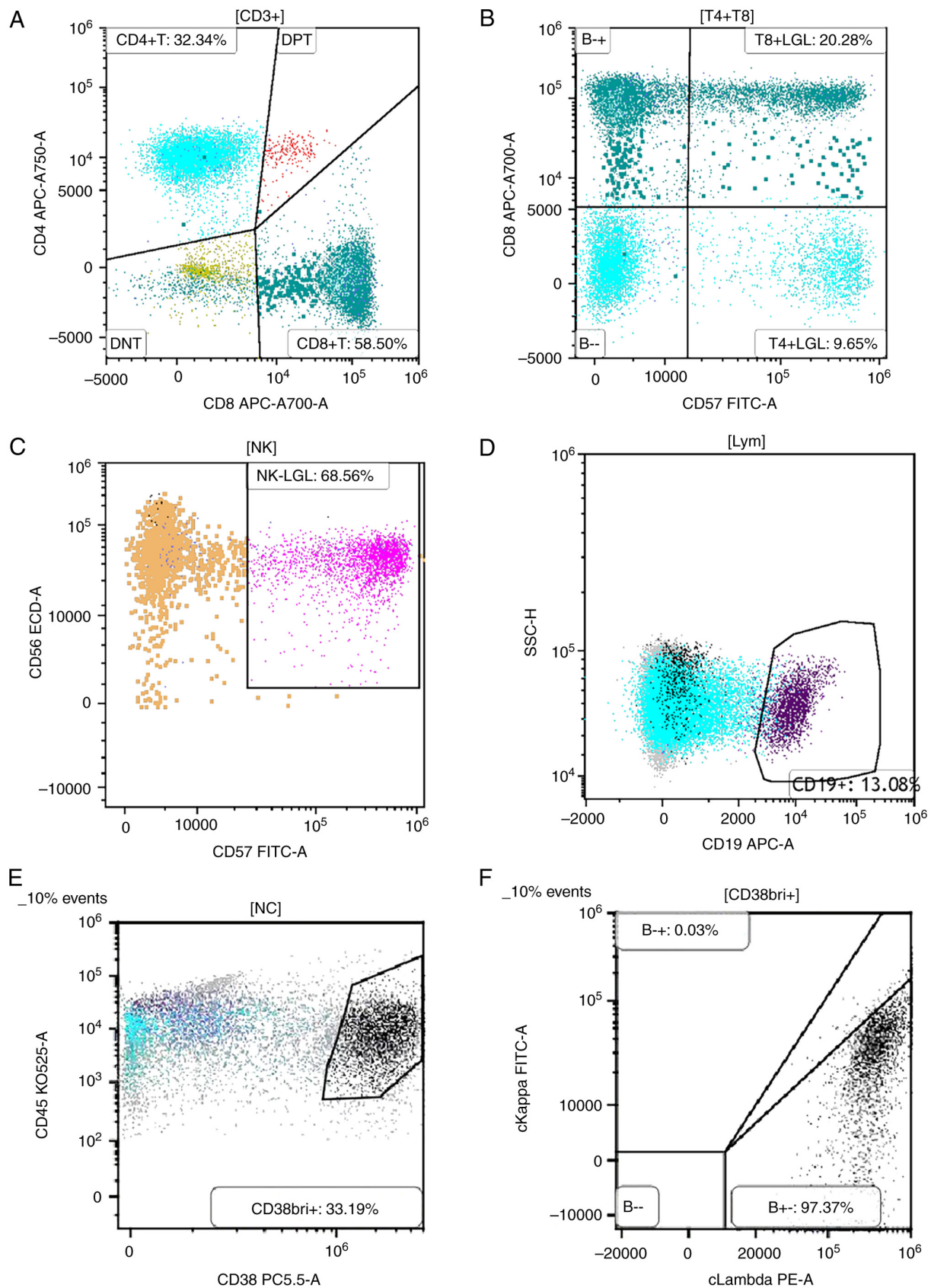


Figure 4. Flow cytometric immunophenotyping of bone marrow cells from a patient with PCM. (A) Lymphocyte analysis showing a decreased CD4/CD8 ratio. (B and C) Quantification of CD57⁺ LGLs, demonstrating a normal proportion of this subset. (D) Marked expansion of plasma cells detected within the bone marrow aspirate. (E) Dual-parameter plot of CD38 and CD45 expression revealing a distinct CD38^{bright}/CD45^{dim} population, accounting for 33.19% of total nucleated cells, consistent with malignant plasma cell infiltration. (F) Intracellular immunoglobulin light chain staining within the CD38^{bright} population indicating prominent λ light chain restriction (97.37%) with minimal κ expression (0.03%), confirming clonal proliferation and supporting the diagnosis of PCM. LGLs, large granular lymphocytes; NC, nucleated cell; PCM, plasma cell myeloma; A, allophycocyanin-Alexa Fluor 700; APC, allophycocyanin; CD38bri⁺, CD38 bright positive; DNT, double negative T cells; DPT, dual-parameter plot; ECD, energy-coupled dye; H, height parameter; KO525, Krome Orange 525; Lym, lymphocytes; NK, natural killer cells; PC5.5, phycoerythrin-cyanine 5.5; PE, phycoerythrin; SSC, side scatter.

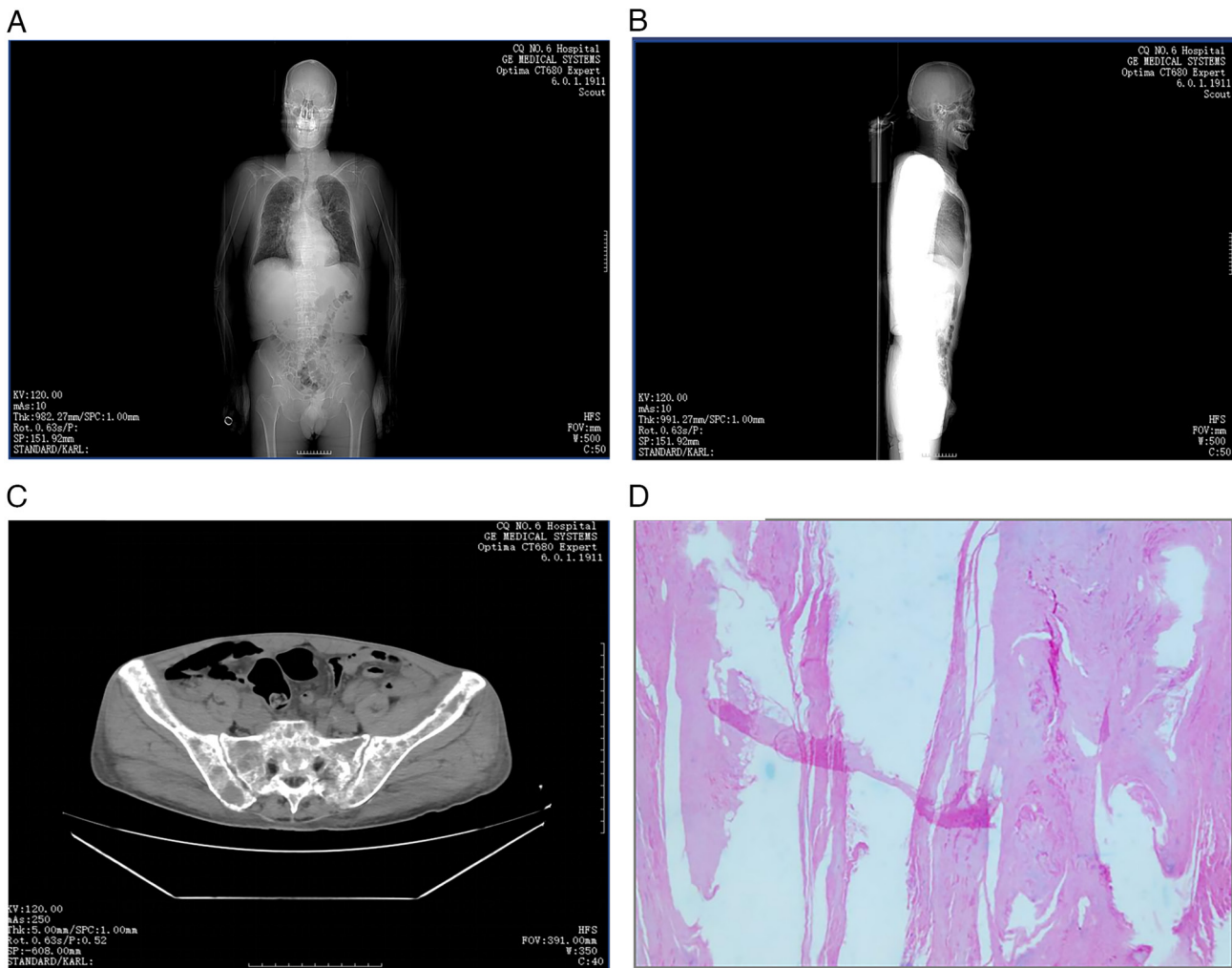


Figure 5. Comprehensive imaging and histopathological evaluation. (A) An anterior scout image from CT demonstrated diffuse skeletal involvement, including multiple hypodense lesions in the skull, ribs, spine, scapulae and pelvis, consistent with lytic lesions seen in multiple myeloma. Bilateral pulmonary infections and pleural thickening were also visible. (B) A lateral scout image further illustrated spinal abnormalities, including compression of the T12 vertebral body and suspected Hsu-Mo nodule at T1, as well as degenerative spinal changes. (C) An axial pelvic CT revealed lytic bone lesions, bilateral pathological rib fractures and pelvic effusion. (D) Histopathological examination of a skin lesion showed squamous epithelium with marked hyperkeratosis (hematoxylin and eosin staining; original magnification, x100), supporting dermatopathological involvement.

topical, applied as needed), for moisturizing and treating dry, flaky skin, a complication arising from systemic treatment and disease progression; and vi) blood transfusions (two units of packed red blood cells, intravenous infusion) administered for symptomatic anemia, which was necessary due to the patient's worsening hematological parameters. These treatments were provided in conjunction with ongoing monitoring and adjustments to the supportive care plan based on the patient's clinical response.

ii) 20 days post-admission: The patient presented with cutaneous manifestations characterized by the emergence of follicular spicules, suggestive of a dermatological response possibly associated with the underlying hematological or renal pathology. The patient received the same treatment as aforementioned, namely, levothyroxine sodium tablets (for hypothyroidism), esomeprazole (proton pump inhibitor for gastric protection), urotoxin (for renal support), nadex cream (for dermatological lesions) and urea cream (for skin hydration). In addition, blood transfusion was provided to address persistent anemia.

iii) 23 days post-admission: Microbiological testing was conducted on a sputum sample using standard bacteriological culture techniques. The specimen was cultured on chocolate agar and incubated under 5% CO₂ at 37°C for 24-48 h. Bacterial identification was performed using Gram staining and confirmed with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Haemophilus influenzae* was isolated, indicating a lower respiratory tract infection. The patient was treated with ceftriaxone (2 g/day, intravenous infusion, for 5 days) targeting the identified pathogen. Blood and platelet transfusions were also administered to manage anemia and thrombocytopenia. Additionally, a sputum cytology specimen was processed and stained using Hetrox-Papanicolaou staining was performed at room temperature (20-25°C) for 15 min for cytological evaluation. The result revealed numerous neutrophils and degenerating epithelial cells, consistent with an active infectious process.

iv) 30 to 33 days post-admission: The patient developed type II respiratory failure, characterized by hypercapnia and hypoxemia, necessitating transfer to the Intensive Care Unit.

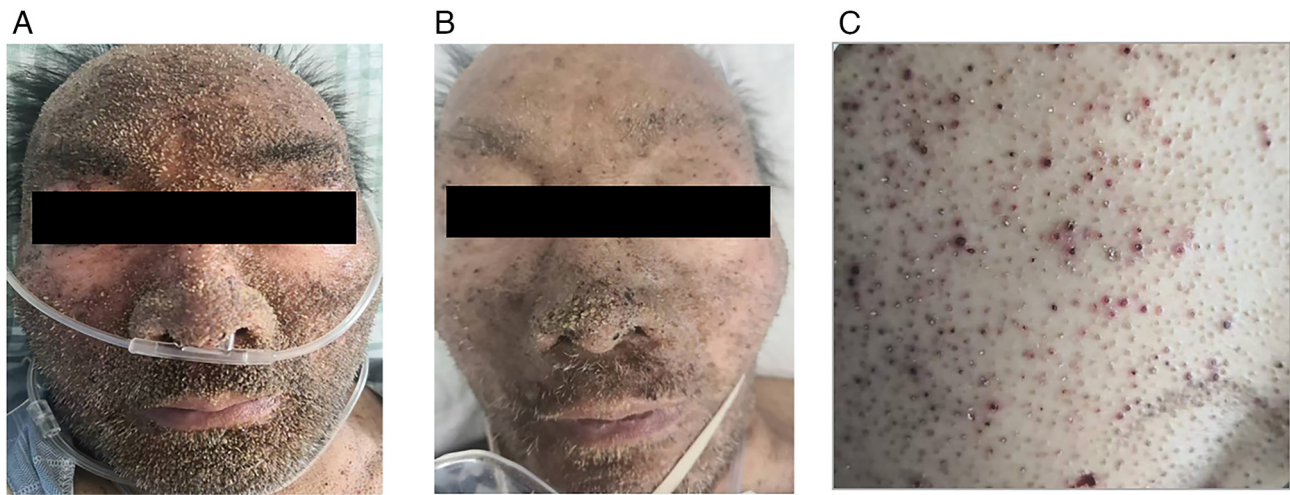


Figure 6. Clinical progression of cutaneous manifestations and therapeutic response. (A) Pre-treatment image of the face showing widespread scaling and crusted lesions. (B) Post-treatment image of the same area with notable resolution of lesions following systemic corticosteroid therapy. (C) Chest lesions showing follicular keratotic papules and erythematous pinpoint eruptions, consistent with follicular spicules of multiple myeloma.

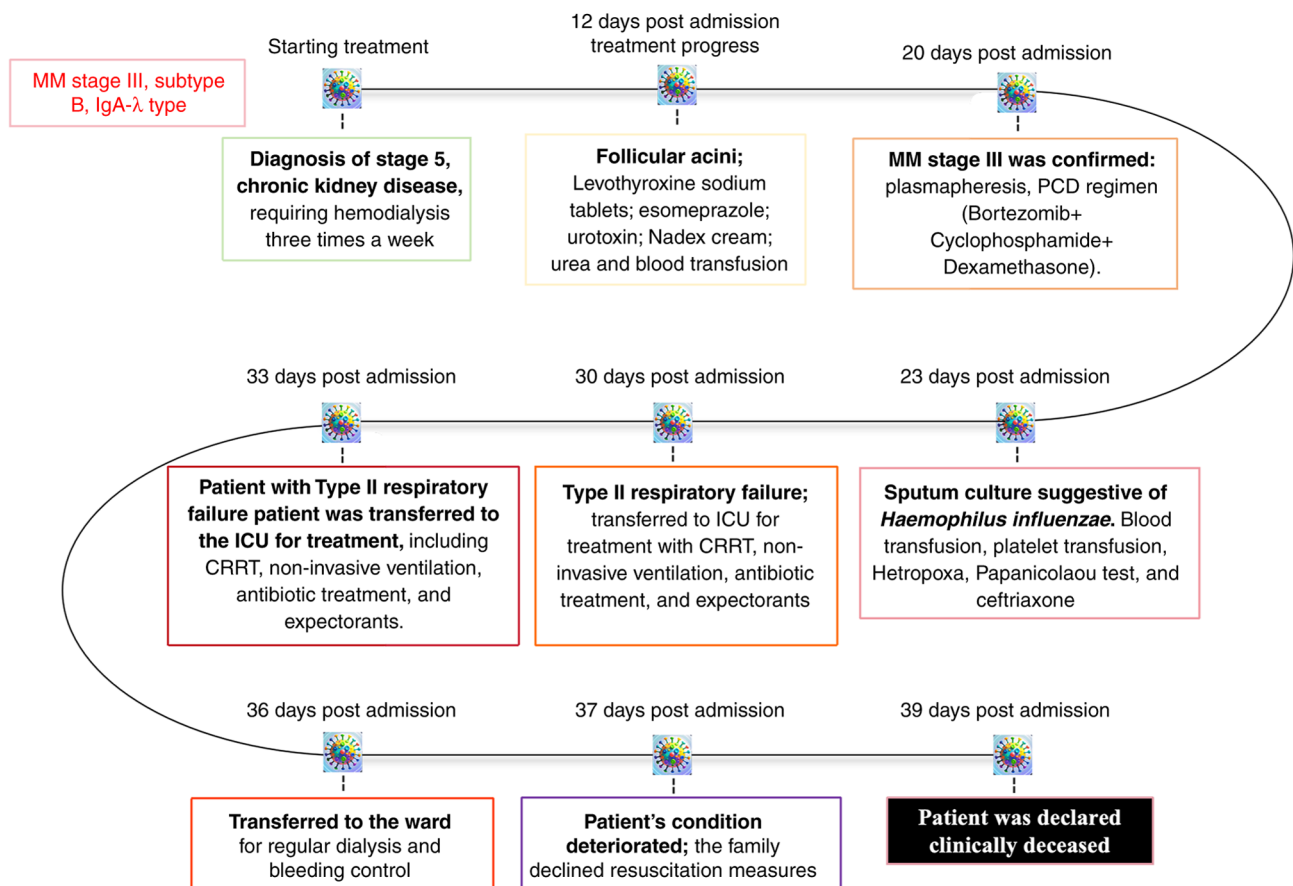


Figure 7. Timeline of clinical course and interventions in a patient with IgA-λ type MM. The patient was diagnosed with stage III MM (subtype B, IgA-λ type) and regular hemodialysis was initiated. In March 2024, follicular acanthosis was noted; treatment included levothyroxine, esomeprazole, urotropine, urea cream, nadifloxacin cream and blood transfusion. In April 2024, the patient developed type II expiratory failure and was admitted to the ICU for CRRT, non-invasive ventilator support, and symptomatic management. Despite intensive care, the patient succumbed to disease-related complications. CRRT, continuous renal replacement therapy; ICU, Intensive Care Unit; MM, multiple myeloma.

Treatment included continuous renal replacement therapy for metabolic stabilization, and non-invasive mechanical ventilation (BiPAP mode, FiO₂ 40-60%) to support respiratory function. Pharmacological management comprised

of the following: i) Broad-spectrum antibiotics, including piperacillin-tazobactam (4.5 g IV every 8 h) to empirically cover gram-negative and anaerobic pathogens pending culture results; ii) moxifloxacin (400 mg IV once daily) to provide

additional coverage for atypical respiratory organisms; and iii) mucolytic therapy, including acetylcysteine (600 mg oral, three times daily), to reduce mucus viscosity and improve airway clearance. Despite these interventions, the patient's respiratory compromise persisted, with ongoing oxygen dependence and elevated arterial CO₂ levels, indicating progressive ventilatory failure.

v) 36 days post admission: Following partial stabilization, the patient was transferred back to the general ward, and continued on regular hemodialysis and received care for recurrent bleeding episodes.

vi) 37 days post admission: The clinical status of the patient deteriorated again. After a discussion with the family, a do-not-resuscitate order was established and aggressive life-sustaining interventions were withheld.

vii) 39 days post admission: The patient was pronounced clinically deceased.

Discussion

The diagnosis of FSMM necessitates the exclusion of other dermatoses that can present with similar follicular hyperkeratotic features. Conditions such as vitamin A deficiency may lead to follicular hyperkeratosis, but they are often accompanied by xerosis and ocular findings such as Bitot's spots (19). In the present case, the serum vitamin A levels of the patient were normal and no ocular signs were present. HIV-associated follicular hyperkeratosis, particularly in cases of advanced immunosuppression, can clinically mimic FSMM; however, the patient tested negative for HIV via both serological and molecular methods, and exhibited no signs of immunodeficiency (20,21).

Skin manifestations related to chronic renal failure, such as prurigo nodularis and perforating dermatoses, may involve follicular lesions; however, these lack the distinct histopathological characteristics of FSMM, including intrafollicular monoclonal protein deposition (22). Additionally, disorders such as acanthosis nigricans and lichen spinulosus can present with spiny papules but do not exhibit the immunoglobulin deposition typical of FSMM (23). Thus, the definitive diagnosis in the present case was supported by the presence of monoclonal immunoglobulin λ light chain deposition in the follicular epithelium, along with plasma cell-rich dermal infiltrates, consistent with the known PCM of the patient.

The pathophysiology of FSMM remains incompletely understood. Current evidence suggests that monoclonal immunoglobulins, particularly light chains secreted by clonal plasma cells, are deposited within follicular structures, leading to epithelial disruption and reactive hyperkeratosis. These deposits may also undergo conformational changes, promoting amyloidogenesis and contributing to the formation of follicular spicules (24,25).

Notably, not all patients with MM develop FSMM. According to a previous study, follicular spicules associated with FSMM occur in <1% of patients with MM, highlighting its rarity and the likelihood that additional host or environmental factors, such as serum paraprotein concentration, the structural properties of light chains or the local skin microenvironment, may influence susceptibility (26). In the current case, skin biopsy revealed follicular hyperkeratosis

with prominent λ light chain deposition, consistent with this hypothesized mechanism. The absence of cryoglobulinemia was confirmed by both negative cryoglobulin screening in serum at 4°C and a lack of clinical symptoms typically associated with cryoglobulinemia, indicating that cold-precipitable immunoglobulins are not essential for FSMM development.

In the present case report, the comorbid end-stage CKD and long-term hemodialysis introduced additional diagnostic complexity. CKD is associated with a broad spectrum of dermatological manifestations, including uremic pruritus, perforating dermatoses and calciphylaxis. However, these CKD-related dermatoses differ significantly from FSMM in both clinical manifestations and histopathological features (27).

Calciphylaxis typically manifests with painful, ulcerative lesions in areas of adiposity and vascular calcification, whereas uremic pruritus lacks follicular-based histological findings. Notably, monoclonal immunoglobulin deposition is rarely observed in CKD-related dermatoses (28). Therefore, the presence of immunoglobulin light chains within follicular structures in the present case strongly supports the diagnosis of FSMM over other CKD-related skin disorders (29).

The present case illustrates the clinical value of recognizing FSMM as a cutaneous marker of plasma cell dyscrasia. FSMM may precede systemic symptoms, serve as a sign of disease relapse or reflect a poor prognosis. Recognition of its characteristic morphology, together with timely histological and immunofluorescence evaluation, can enable early diagnosis and guide therapeutic decisions.

Novel learning points from the present case include: i) FSMM may occur independently of cryoglobulinemia, challenging earlier assumptions (30); ii) immunoglobulin light chain deposition can be a key distinguishing factor in patients with comorbid renal disease; and iii) FSMM serves as a potential non-invasive biomarker for disease activity in MM. Had the condition of the patient stabilized, long-term management could have included systemic anti-myeloma therapy adapted for renal impairment, topical keratolytics or retinoids for symptom control, and regular dermatological monitoring to assess treatment response. Nutritional support and optimization of dialysis care may also contribute to maintaining skin integrity (31).

In conclusion, FSMM should be considered in patients with unexplained follicular hyperkeratosis and suspected or confirmed plasma cell neoplasms. Dermatological manifestations in such patients warrant thorough evaluation, including biopsy and immunoglobulin profiling. Further research is needed to clarify the mechanisms underlying FSMM, and to establish standardized diagnostic and therapeutic approaches.

Acknowledgements

The authors would like to express their sincere gratitude to the late Dr Junling Tang (Department of Occupational Disease and Poisoning Medicine, The First Affiliated Hospital of Chongqing Medical and Pharmaceutical College, Chongqing, China) for their early involvement in the clinical evaluation and patient management in this case. These contributions laid the foundation for the development of this report. The authors would also like to thank Mr. Zhenjun

Xi and Ms. Qianqian Liu (Department of Occupational Disease and Poisoning Medicine, The First Affiliated Hospital of Chongqing Medical and Pharmaceutical College, Chongqing, China) for their invaluable contributions to the data collection and experimental process; their meticulous efforts ensured the accuracy and reliability of our research findings. Additionally, the authors are grateful to Mrs. Li Yan and Mr. Lvsu Ye (Department of Occupational Disease and Poisoning Medicine, The First Affiliated Hospital of Chongqing Medical and Pharmaceutical College, Chongqing, China) for their assistance in data analysis and interpretation, which greatly enhanced the depth and quality of the research outcomes.

Funding

The authors declare that financial support was received for the research, authorship and publication of this article. The work was funded by the Chongqing Medical Scientific Research Project (Joint Project of Chongqing Health Commission and Science and Technology Bureau) (grant nos. 2023GGXM006, 2024ZDXM026 and 2024ZDXM026), the Key Research Project from Chongqing Medical and Pharmaceutical Vocational Education Group (grant no. CQZJ202329), the Chongqing Key Municipal Public Health Specialty Construction Project, 2024 Scientific Research Project of Chongqing Medical and Pharmaceutical College (grant no. ygzrc2024101), the Chongqing Education Commission Natural Science Foundation (grant no. KJQN202402821), the Chongqing Shapingba District Science and Technology Bureau Project (grant no. 2024071), the 2024 Chongqing Medical and Pharmaceutical College Innovation Research Group Project (grant no. ygz2024401), and the Chongqing Science and Health Joint Medical Research Project (grant no. 2024SQKWLHMS051).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XiL and XuL designed the study and coordinated the clinical evaluation. QinL, QiaL and XuL participated in the diagnosis and treatment of the patient. XiL, QiaL and QinL were responsible for data collection, clinical interpretation and histological assessments. YL, LZ and LW contributed to the analysis and interpretation of the laboratory and imaging data, and supervised the study. All authors participated in the writing of the original draft and figure preparation. YL, LZ and LW critically reviewed and revised the manuscript. XiL and YL confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of clinical details and any accompanying images. The patient was fully informed about the purpose of the publication and explicitly consented to the use of facial photographs and other potentially identifiable data. The consent included acknowledgment that the images may be published in scientific journals and disseminated online in an academic context. Efforts have been made to ensure patient anonymity where possible, while recognizing that complete anonymity cannot be guaranteed in cases involving facial features.

Competing interests

The authors declare that they have no competing interests.

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