

Unusual Presentation of Multiple Myeloma: A Case Series

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Abstract

Introduction: Multiple myeloma is the most common bone malignancy characterized by malignant proliferation of plasma cells leading to production of a monoclonal paraprotein. Varied clinical presentations are noted in the patients like fever, fatigue, weight loss, paraesthesias, hypercalcemia, hyperviscosity, renal failure, bone pain or pathological fractures, cutaneous lesions, etc. We present a series of multiple myeloma cases with unusual presentation over a period of 3 years. **Aims & Objective:** To study the unusual clinico-hematological and histopathological presentation in patients with multiple myeloma. **Materials & methods:** In this study, we reviewed bone marrow aspirate & biopsy slides in our hospital from May 2014 to June 2017. Patients diagnosed with multiple myeloma were selected. The patients' clinical information, hematological and histological findings were obtained from the medical records department and correlation was done. **Results:** We found a total of 11 cases of multiple myeloma with unusual and rare presentations. Proper clinical, radiological, hematological and histopathological correlation was done before giving a final diagnosis in these cases. Unusual cutaneous and gastrointestinal involvement of multiple myeloma was noted, especially in younger individual, making our study much rarer. **Conclusion:** Multiple myeloma is a debilitating malignancy. In the past few years, substantial progress has been noted in treatment of this entity. Early diagnosis of multiple myeloma along with appropriate management will prevent serious complications, especially in younger individuals. The present case series attempts to make an effort to study the clinicopathological correlation in cases of multiple myeloma and associated rare and unusual presentations.

Keywords: Myeloma; Lytic lesions; Bone marrow; Congo red; Amyloid tumor

Introduction

Multiple myeloma is a malignant plasma cell neoplasm leading to monoclonal proliferation of paraprotein.^[1] There can be varied clinical and hematological presentations in patients with multiple myeloma ranging from hypercalcemia, hyperviscosity to bone pains/fractures and even renal failure.^[1,2] However, sometimes patients with multiple myeloma can be asymptomatic or present with uncommon clinical findings. We noted rare presentations of amyloidosis in multiple myeloma in young individuals. A rare case of synchronous malignancy was also noted. In this case series, we attempt to study the cases of multiple myeloma with rare and unusual findings.

Materials and Methods

In this study, we reviewed bone marrow aspirate & biopsy slides in our hospital from May 2014 to June 2017. Patients diagnosed with multiple myeloma were selected. The diagnosis of multiple myeloma was made based on the following parameters (as in WHO classification): $\geq 10\%$ monoclonal plasma cells in bone marrow, monoclonal protein in serum and/ urine, one or more myeloma related organ damage like hypercalcemia, anemia, lytic bone lesions and kidney biopsy diagnosis of paraprotein-associated lesion like amyloidosis, cast nephropathy. The diagnosis of amyloidosis was done on the presence of fibrillar Congo-red positive deposits in the kidney. The patients' clinical information including the demographic details, renal clinical and laboratory findings, i.e. complete blood counts, serum calcium, serum proteins, renal function test, X-ray,

Ultrasound, serum protein electrophoresis, urinary Bence Jones proteins along with bone marrow aspirate & biopsy report with immunohistochemistry were obtained from the medical records department and correlation was done. The cases with unusual clinical and hematological parameters along with histopathological findings were selected and results tabulated.

Results

A total of 58 cases of multiple myeloma were retrieved from the database, of which 39 were males and 19 females (M: F:2: 1). The age of the patients ranged from 28 to 87 years with mean age being 58.91 years. The common presenting symptoms were fever, fatigability, lower limb weakness, bone pain and chronic backache in most of the patients. Other presentations noted were decreased appetite, cough, breathlessness, pedal edema, generalized anasarca, altered sensorium, decreased urinary output, loose stools, bodyache and pathological fractures.

We found a total of 11 cases of multiple myeloma with unusual and rare presentations. The total 11 cases are discussed as below and summarized in Table 1 as well.

In the first case, a 28-year-old male presented with complaints

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of pain abdomen, vomiting and hematemesis. His routine blood examination was within normal limit except for an increase in Erythrocyte sedimentation rate (40mm at the end of 1st hour). Bence Jones protein was not detected; however monoclonal gammopathy (M spike) was noted on serum protein electrophoresis in gamma globulin region. His renal function test was deranged with elevated levels of serum urea (34 mg/dl) and creatinine (6 mg/dl). Serum protein showed decreased albumin levels with A: G reversal (A:G: 1:1.6). X-ray skull & pelvis showed multiple lytic lesions [Figures 1c & 1d]. Bone marrow aspiration and biopsy showed complete replacement of normal hematopoietic elements with sheets of plasma cells along with scattered plasmablasts [Figures 2c & 2d]. These findings were confirmed with CD138 immunohistochemistry.

Colonoscopy showed evidence of pancolitis with few ulcers in ileum along with thickened folds in caecum [Figures 1a & 1b]. The histopathological examination of thickened areas of ileocecal region and gastric mucosa showed deposition of acellular pale eosinophilic material which was congophilic when stained with congo red and showed apple green birefringence on polarized light [Figures 2a & 2b]. An impression of "Amyloidosis" was given. This was an interesting case of multiple myeloma in a young individual who initially presented with extensive gastrointestinal amyloidosis.

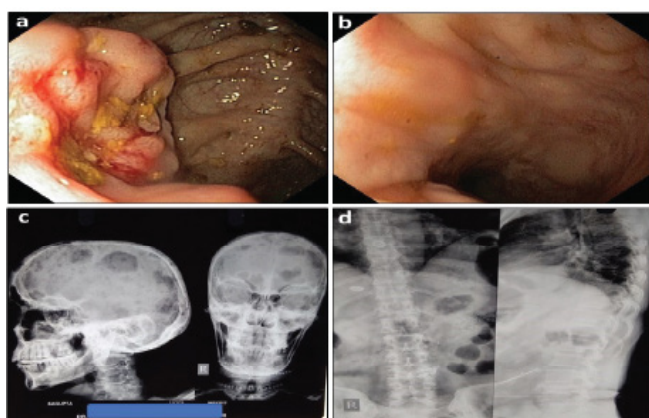


Figure 1: a & b - Colonoscopy images showing scattered ulcers in colon and ileum with loss of vascular pattern, suggestive of Inflammatory Bowel Disease (IBD). c & d - X-ray skull and vertebra revealing multiple lytic lesions.

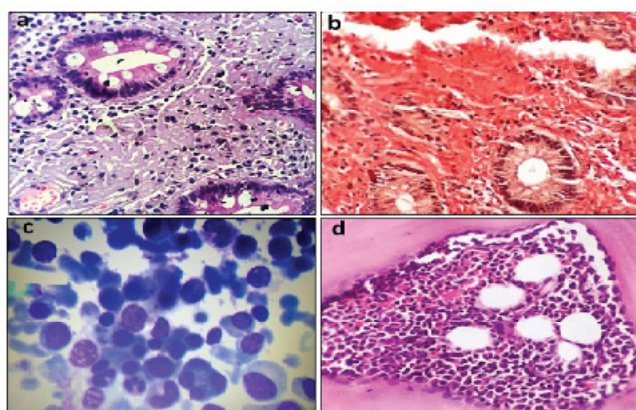


Figure 2: a - Section from stomach showing amyloid deposits interspersed between the glands (H & E, 200x). b - Section showing Congo red positivity (200x). c & d - BMA smears and biopsy showing plasma cells, with few binucleate and multinucleate forms and plasmablasts (c-Giemsa, 400x; d - H & E, 200x).

Another, very interesting case was noted in young male, aged 30 years, who was suffering from chronic renal disease for past 2 years along with significant weight loss. Multiple subcutaneous swellings were noted on bilateral gluteal region, face, elbow and left humerus [Figures 3a & 3b]. Multiple hypopigmented skin lesions were also noted over face and back.

X-ray showed multiple lytic lesions in diaphysial region of bilateral humerus, bilateral femur and skull. Hypercalcemia and an increase in ESR of 140 mm at the end of 1st hour were noted. His renal function test was deranged with elevated urea (168 mg/dl) and creatinine (8.1 mg/dl) levels. Serum protein electrophoresis showed monoclonal peak in Beta2 region.

Fine needle aspiration smears from the multiple cutaneous swelling showed many multinucleated osteoclastic giant cells along with areas of necrosis & calcification. Histopathological examination from one of the swellings revealed fibrocollagenous tissue with pink acellular amorphous material (positive for Methyl violet and Congo red) with scattered chondrocytes and chondroid matrix [Figures 3c & 3d]. A diagnosis of "amyloid tumor" was given.

Bone marrow aspiration smears showed marked increase in plasma cells (50-55% of nucleated cells) along with few binucleated, multinucleated forms and immature plasma cells including plasmablasts. This is a very rare presentation of multiple myeloma in a younger individual with amyloidoma of skin as the initial presentation.

We also noted an elderly female presented with chronic renal disease and deranged kidney function tests (urea- 60 mg/dl and creatinine - 7 mg/dl). Interestingly, her calcium and ESR levels were found to be within normal limit; however, M spike was noted on serum protein electrophoresis. Her renal biopsy showed increase in mesangial matrix and cystic dilatation of tubules showing granular, RBCs, WBCs and fractured casts in the lumen. A diagnosis of "cast nephropathy" was made. Bone marrow examination showed 40-45% plasma cells with few immature forms and plasmablasts. This case highlights the importance of diagnosing cast nephropathy on histology which further helps in evaluating the patient with underlying multiple myeloma.

A 50-year-old male presented to hospital with lower backache,

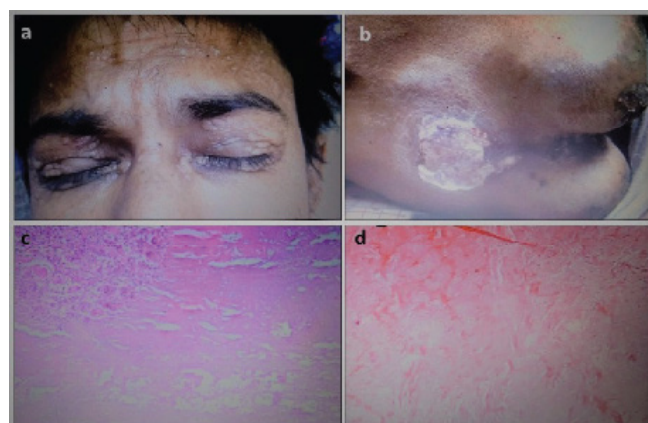


Figure 3: a & b - Cutaneous amyloid deposits over face, buttock & lower back. c: H & E image revealing fibrocollagenous tissue with pink acellular amorphous material bounded by histiocytes and foreign body giant cells (H & E, 200x). d: Image showing Congo red positivity, confirming diagnosis of amyloid tumor (Congo red, 200x).

weakness in upper and lower limbs along with loss of sensation. Ultrasound and MRI revealed evidence of compression fracture of D1-D3. Biopsy from D2-D4 pedicle showed histological features of plasmacytoma.

On further investigations, serum protein electrophoresis showed monoclonal spike (M band). His renal function tests were deranged with elevated urea (155 mg/dl) and creatinine (4.5 mg/dl) levels. A reversal of albumin globulin ratio was noted with increase in globulin levels (A:G: 1:2). However, her calcium level was within normal limit. Bone marrow examination revealed presence of more than 40% plasma cells including immature forms and few plasmablasts. In this case, the patient initially presented with solitary plasmacytoma. On further investigations, a diagnosis of multiple myeloma was made.

In our series, a 45-year-old female presented to hospital with firm to hard swelling on the left clavicular region along with weakness and pain abdomen [Figure 4a]. CECT showed lytic expansile lesion with calcification & soft tissue attenuation in left medial clavicle [Figure 4b]. X-ray skull showing multiple lytic lesions [Figure 4c]. Fine needle aspiration from the clavicular region showed scattered cells with eccentric nuclei, coarse chromatin, prominent nucleoli, perinuclear clear space and deep blue cytoplasm, suggestive of plasma cells [Figure 4d]. Cell block was prepared from cytology aspirate (H&E), revealed an occasional group of tumor cells with CD 138 [Figures 4e & 4f]. A diagnosis of Anaplastic myeloma was given. These findings led to further investigations to rule out multiple myeloma.

Her renal function tests were within normal limits, serum protein electrophoresis showed M spike in gamma globulin region. Bone marrow plasmacytosis with 50% of plasma cells along with presence of M band in gamma-globulin region in SPE confirmed it to be a case of multiple myeloma.

In the present series, an 80-year-old female presented to hospital with altered sensorium. She was diagnosed with carcinoma breast 5 years back for which she had undergone radical mastectomy. On further investigation, renal function test was deranged with marked elevation of urea (160 mg/dl) and creatinine (14 mg/dl). However, her calcium level was within normal limit. Her

protein levels were elevated with raised globulin levels. In view of deranged kidney function tests and A: G reversal, serum protein electrophoresis was done which showed evidence of M spike. Subsequently, bone marrow aspiration and biopsy showed increase in plasma cells (>45%), suggestive of multiple myeloma. In this case, two different malignancies were noted in the same individual making it a rarer presentation.

A 60-year-old female presented with a left parietal scalp swelling for last 8 months, on & off headache and chest pain. The swelling measured approximately 4 × 4 cm and was hard in consistency. CECT chest showed extensive destruction of multiple dorso-lumbar vertebrae and consolidation in right middle lobe of lung. CT brain showed a 3 × 3.6 cm sized hyperdense enhancing space occupying lesion arising from the dura, vault at left parietal convexity, suggestive of Meningioma. MRI brain revealed extra-axial homogeneously enhancing solid lesion measuring 3.8 × 2.6 cm in left parietal lesion involving skull vault and scalp.

Fine needle aspiration cytology smears from the lesion showed numerous plasma cells along with few atypical forms. A possibility of plasma cell lesion could not be ruled out. Histological examination of the skull bone lesion showed sheets of plasma cells with membranous positivity for CD138. An impression of plasmacytoma was given. Further, bone marrow examination was done and showed marked prominence of plasma cells, constituting 42% of all nucleated cells. In view of the clinical profile (presence of lytic lesion, anemia), serum protein electrophoresis (positive M band), bone marrow aspiration smears and biopsy, the diagnosis of plasma cell myeloma was made. This case is being presented here because of the unusual presenting features like chest pain, on & off headache and consolidation in lung. These symptoms pointed initially towards a metastatic lesion to scalp from an underlying malignancy or it could be because of meningioma, as suggested on CECT. However, FNAC & bone marrow examination helped in making a correct diagnosis of plasmacytoma.

We also noted 4 cases of multiple myeloma where patients presented with mild lower backache and weakness but had no lytic lesions on X-ray. Their renal function tests and calcium levels were also within normal limits and no M spike was noted. However, bone marrow aspirate and biopsy specimens in these patients showed presence of more than 70% plasma cells including immature forms & few plasmablasts suggestive of multiple myeloma.

Discussion

Multiple myeloma is a malignant neoplasm characterized by formation of malignant plasma cells. Usually, few plasma cells are found in the bone marrow and they constitute an important part of body's immune system, working together with other several types of cells to fight infections and other diseases.^[1] Initially, patients are often asymptomatic. However, with advancement of disease process, patients present with bone pain, bleeding, frequent infections, anemia, etc. Rarely, complications may occur in patients like amyloidosis, etc. The exact etiology of multiple myeloma is not known. However, various risk factors like alcohol, obesity have been implicated in its genesis.

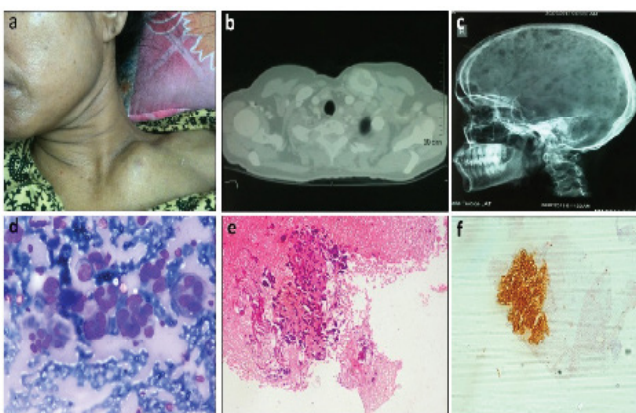


Figure 4: a - A firm to hard swelling in left clavicular region, b - CECT showing lytic expansile lesion with calcification & soft tissue attenuation in left medial clavicle. c - X-ray skull showing multiple lytic lesions. d - Smear showing scattered cells with eccentric nuclei, coarse chromatin, prominent nucleoli, perinuclear clear space and deep blue cytoplasm, suggestive of plasma cells (Pap, 400x). e & f - Cell block was prepared from cytology aspirate (H&E, 200x), revealed a single group of tumor cells with CD 138 (200x).

Table 1: Total of 11 cases of multiple myeloma with unusual and rare presentations

Important findings	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8-11
C/F	28/M, Pain abdomen, vomiting, fever. Colonoscopy: Pancolitis	30/M, k/c/o CKD. Multiple subcutaneous swelling on B/L gluteal regions, face, elbow, left arm.	Elderly female with k/c/o CKD & deranged KFT	50/M, lower backache, weakness in U/L & L/L. USG & MRI: D2-D3 compression	45/F, hard swelling over left clavicular region. CECT: lytic expansile lesion with calcification in left medial clavicle	80/F, altered sensorium. k/c/o Ca breast & operated 5 years back.	60/F, left parietal swelling with headache & chest pain. CECT chest: extensive destruction of multiple dorso-lumbar vertebrae. MRI brain: extra-axial homogeneously enhancing solid lesion in left parietal lesion involving skull vault and scalp.	4 patients with lower backache and weakness. Normal KFT, Calcium. No bony lytic lesions.
HPE	Extensive gastrointestinal amyloidosis	Amyloid tumor	Renal biopsy: Cast Nephropathy	Biopsy from D2-D3 region: Plasmacytoma	Cell block from clavicular region swelling: Anaplastic myeloma	k/c/o of IDC breast.	Cell block from scalp swelling: Plasmacytoma.	---
BMA & BMB	>90% plasma cells with plasmablasts	>55% plasma cells including plasmablasts.	>50% plasma cells including immature forms.	>40% of plasma cells with plasmablasts	>50% plasma cells including immature forms.	>50% plasma cells with plasmablasts.	>42% plasma cells including the immature forms.	>70% plasma cells including plasmablasts.
SPE	M-spike in gamma-globulin region.	Monoclonal peak in Beta-2-region.	M spike noted.	M spike noted	M band in gamma-globulin region.	M spike noted.	M band noted.	No M-band was noted.

Abbreviations: C/F: Clinical Features, HPE: Histopathological Examination, BMA & BMB: Bone Marrow Aspiration And Biopsy, CKD: Chronic Kidney Disease, U/L: Upper Limb, L/L: Lower Limb, IDC: Infiltrating Ductal Carcinoma, KFT: Kidney Function Test

In multiple myeloma, there is overproduction of one type of abnormal immunoglobulin, thereby putting myeloma patient at risk of developing amyloidosis. A crucial point to remember is that not all patients with multiple myeloma will develop amyloidosis. It has been studied that approximately 35% of myeloma patients will develop amyloidosis at some point, however only 10-15% will experience symptoms associated with it.^[2] The symptoms of amyloidosis will depend upon which organs are involved and how much quantity of protein has been accumulated. The patients can present with loss of appetite, diarrhea when light chains accumulate in intestine. The treatment of amyloidosis with myeloma is more challenging than myeloma alone due to associated organ damage in the patients.^[3]

In the present study, we noted a case of multiple myeloma with extensive gastro-intestinal amyloidosis in a young male patient. He presented with pain abdomen, hematemesis. His biochemical, hematological and radiological parameters were suggestive of multiple myeloma and were confirmed on bone marrow examination & serum protein electrophoresis. Multiple sections from gastric and duodenal biopsy showed evidence of extensive gastro-intestinal amyloidosis. A similar case of gastro-intestinal amyloidosis with multiple myeloma was reported by Gjeorgilevski et al.^[4] in a 52-year-old male patient who presented with rectal bleeding. However, we noted this presentation in younger individual, making it much more unusual presentation. Prognosis of such cases is bad, as noted in our study as well as by Gjeorgilevski et al.^[4] as in both patients succumbed to the illness.

Skin manifestation in myeloma associated amyloidosis depends upon the site of amyloid deposition.^[5-7] Common sites of involvement are eyelids, retroauricular region, neck, axillae, inframammary area, umbilicus, inguinal and anogenital regions. However, lesions may also be seen on central face, lips, tongue & buccal mucosa. Our patient presented with multiple subcutaneous swellings on bilateral gluteal region, elbow and left humerus. Multiple hypopigmented skin lesions were also noted over face and back. A similar case report was published by Kumar et al.^[7] where patient presented with multiple, non-itchy, popular lesions in lower eyelids & lower chest wall bilaterally. However, our patient was much younger and had extensive skin involvement which clinically mimicked skin lesions as seen in T-cell leukemia

Myeloma cast nephropathy is histologically defined as formation of plugs (casts) in the renal tubules due to accumulation of immunoglobulin light chains and this can result in renal failure.^[8] This is most common form of kidney disease in multiple myeloma patients. Here, there is co-precipitation of immunoglobulin free light chains (FLCs) with Tamm-Horsfall glycoprotein (THP). Involvement of kidney has a significant consequence on the outcome of these cases.

Treatment has very important implication in these cases. The current therapeutic approaches are focused on reduction of serum free light chains by 50-60% which is required for renal recovery in cast nephropathy patients.^[8] In the present study, we

report a proven case of multiple myeloma with cast nephropathy in renal biopsy.

We noted three cases of plasmacytoma, one on left clavicle bone which was diagnosed on fine needle aspiration cytology and biopsy. The second case was located on D2-D3 vertebrae and the third case was a scalp swelling on the parietal area. Initially, cytological and histological examination of swelling showed evidence of plasmacytoma. On further investigation, i.e., bone marrow examination and SPE, diagnosis of multiple myeloma was made. Solitary bone plasmacytosis (SBP) affects less than 5% of patients with plasma cell myeloma.^[9] Usually these patients present with local symptom and at an early age when compared to multiple myeloma. Over a period of 2-3 years, MM develops in SBP patients. SBP represents an early manifestation of MM in some cases.^[9] In all the three patients, solitary bone lesions were present for more than 2 years.^[9] He was diagnosed with SBP when he came to hospital. Detailed investigations further diagnosed these cases with coexisting multiple myeloma.

Diagnosis of synchronous and metachronous malignancies in a single patient pose a diagnostic challenge. Tumors are labeled as synchronous when the carcinomas occur at the same time or within a period of 2 months of each other whereas term metachronous is used when the cancers follow in sequence more than 2 months apart^[10]. We also noted an 80-year-old female with existing multiple myeloma presenting 4-5 months after diagnosis of infiltrating duct carcinoma in our study. After extensive literature search, it has been found that very few cases have been reported with diagnosis of multiple myeloma and breast cancer.^[10]

Vennepureddy et al.^[10] reported a case with multiple myeloma, breast cancer and monoclonal B-cell lymphocytosis in a 77-year-old female. Ali et al.^[11] reported a case of synchronous diagnosis of MM & breast carcinoma with plasmacytoid morphology on the initial presentation. Multidisciplinary management is required for successfully treating patients with multiple primary malignant metachronous tumors.^[11] This case highlighted the importance of cytomorphologic similarities among hematopoietic & epithelial malignancies, thereby making distinction difficult. It is important to rightly label these different malignancies as they require different modes of intervention and management.

Clinical profile at times are quite deceptive and particularly when patients present without any obvious bony lytic lesion. Majority of our patients (4 out of 11) presented with just mild backache without involvement of any bony lytic lesion or any deranged renal profile. This makes the diagnosis difficult. However, as per the International Myeloma Working Group (IMWG) criteria for diagnosis of multiple myeloma, these patients showed presence of one of the myeloma defining events, MDEs (i.e., presence of more than 60% plasma cell in bone marrow). In addition, these patients showed decreased hemoglobin level of <10 gm/dL as well.

Similarly, some of the unusual presentations like predominance of gastrointestinal manifestations, multiple subcutaneous nodules, conflicting imaging (MRI imaging), normal serum calcium levels and a history of carcinoma breast make the diagnosis of multiple myeloma less tenable.

Conclusion

This study represents a constellation of rare findings in patients with multiple myeloma. These cases showing

unusual presentations highlight the significance of good clinicopathological correlation to arrive at a correct diagnosis. Early diagnosis and management of such cases can decrease the morbidity and mortality thereby negating the complications which can develop further in these patients.

Conflict of Interest

The authors disclose that they have no conflicts of interest.

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