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Multiple Myeloma: A Review

Dr.Wafaa M.Alshehri

Department of Internal Medicine, King Faisal Hospital, Makkah , Saudi Arabia

Abstract: **Multiple myeloma is a plasma cell malignancy involving the bone marrow. Patients may have smoldering (asymptomatic) disease or most of them will present with signs or symptoms related to the infiltration of plasma cells into the bone or other organs or to kidney damage from excess light chains and present with significant morbidity. Prompt recognition of symptomatic multiple myeloma is critical, because delayed diagnosis is associated with increased complications. In this review article we aim to enumerate the clinical presentation, pathophysiology, diagnosis and treatments modalities for multiple myeloma.**

Keywords: **Multiple Myeloma, Monoclonal gammopathy, Plasma cells, bortezomib, Plasmacytoma.**

1. INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 10 percent of all hematologic malignancies. It is an incurable disease and the cause of about 20 percent of deaths from hematologic malignancy and 2 percent of deaths from all cancers. MM is thought to evolve from an asymptomatic premalignant stage of clonal plasma cell proliferation termed monoclonal gammopathy of undetermined significance (MGUS). MGUS is present in over 3 percent of the population above the age of 50, and progresses to myeloma or a related malignancy at a rate of 1 percent per year. While MGUS is asymptomatic, MM is characterized by end-organ damage, which includes hypercalcemia, renal dysfunction, anemia, or lytic bone lesions. In some patients, an intermediate asymptomatic but more advanced premalignant stage referred to as smoldering multiple myeloma (SMM) can be recognized clinically. Patients with MM are given therapies directed at the underlying plasma cell clone with the goal of preventing further complications. In contrast, active treatment is not routinely indicated for patients with MGUS or SMM.High dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT, rescue) is considered a standard of care for eligible patients with newly diagnosed MM.

2. EPIDEMIOLOGY

MM accounts for approximately 1 to 2 percent of all cancers and 10% of all hematologic cancers[1]. The annual incidence in the United States is approximately 4 to 5 per 100,000 [2]. The lifetime risk of getting MM is approximately one in 125 (0.8%). [3] Approximately 12,770 deaths from MM (6,830 in men and 5,940 in women) are expected to occur in 2018. [4] Rates for new MM cases have not changed significantly over the last decade, while death rates fell on average 0.7% each year over 2005-2014. [3] MM occurs in all races and all geographic locations [5]. The incidence varies by ethnicity; the incidence in African Americans and Blacks from Africa is two to three times that in Whites [6-7]. In contrast, the risk is lower in Asians from Japan and in Mexicans [8-9].(Figure1A-C) The median age of patients with MM is 68 years for men and 70 years for women. Only 18% of patients are younger than 50 years, and only 3% of patients are younger than 40 years. The male-to-female ratio in MM is approximately 3:2.

A small but unknown fraction of cases are familial. The risk of developing MM is approximately 3.7-fold higher for persons with a first degree relative with MM [10]. MM has been reported in clusters of two or more first degree relatives, identical twins, and in four members spanning three generations in one family, with an incidence of approximately 3 familial cases per 1000 patients with MM [10-11].

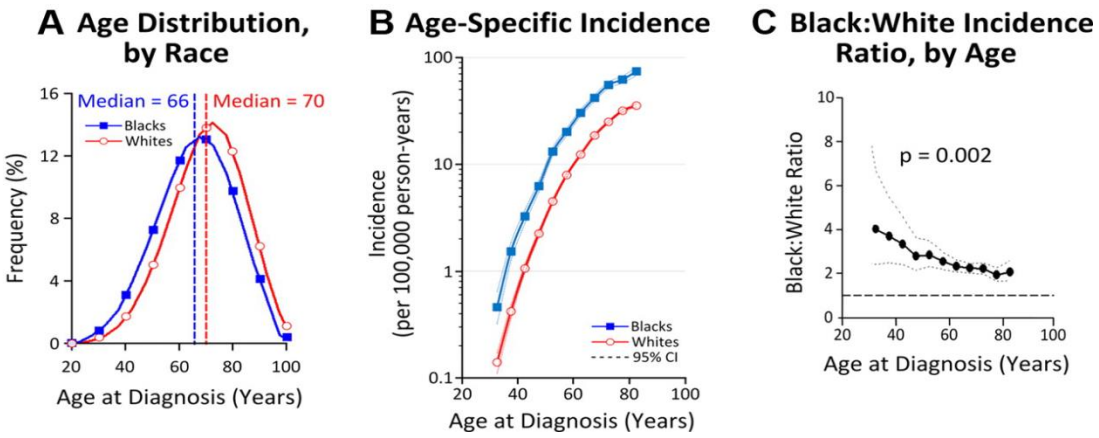


Figure 1: Incidence patterns of MM by race and age, 1973-2005 (SEER-9) byAdam J. Waxman et al. Blood 2010;116:5501-5506.

3. CELL OF ORIGIN AND BIOLOGY

MM appears to arise from the malignant transformation of post-germinal center plasma cells [11-12]. The post-germinal ancestry of these cells is principally supported by the identification of somatic mutations in the variable region of the immunoglobulin genes, which serve as a marker of germinal center transit. These cells also display ongoing somatic mutations, which reflect the pressure of antigen selection encountered by post-germinal center lymphocytes.Primary early chromosomal translocations occur at the immunoglobulin switch region on chromosome 14 (q32.33), which is most commonly juxtaposed to MAF (t[14;16][q32.33;23]) and MMSET on chromosome 4p16.3. This process results in the deregulation of two adjacent genes, MMSET in all cases and FGFR3 in 30% of cases.[13-14]

4. PATHOGENESIS

The first step in the pathway to the development of MM is the establishment of the premalignant plasma cell proliferative disorder known as monoclonal gammopathy of undetermined significance (MGUS). Primary cytogenetic abnormalities appear to play a major role in the development of MGUS. Most, if not all, cases of MGUS and MM have chromosomal abnormalities that can be detected by fluorescence in situ hybridization (FISH), multicolor spectral karyotyping, comparative genomic hybridization, or gene expression profiling [15-16]. The percentage of cases demonstrating each abnormality varies by the detection method used and disease stage. Most cases of MGUS appear to be initiated in conjunction with either translocation events involving the immunoglobulin heavy chain (IgH) locus (approximately 40 percent) or genetic instability manifested by trisomies (approximately 40 percent) or both translocations and trisomies (approximately 10 percent) [17-18].

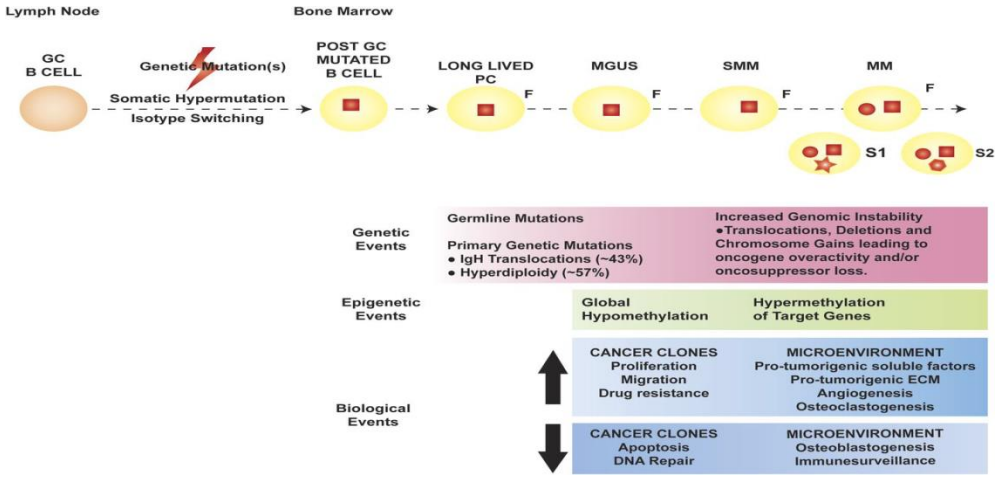


Figure 2: Pathogenesis of MM. The orange round cell represents a normal B cell, whereas the yellow round cell is a mutated, post–germinal center (GC) B lymphocyte that later differentiates into a long-lived PC (yellow oval). In MM pathogenesis, the initial genetic event (red square) is thought to occur in the GC, facilitated by the processes of somatic hypermutation and isotype switching, and characterizes the founder clone (F).

5. PROGRESSION OF MGUS TO MM

Since not all patients with monoclonal gammopathy of undetermined significance (MGUS) develop MM, the initial genetic changes resulting in MGUS are necessary but not sufficient for the development of MM. MGUS progresses to symptomatic MM at a consistent annual rate suggesting that this progression may be explained by a "random second hit" model [19]. The risk of progression is similar regardless of the known duration of antecedent MGUS, suggesting that the second-hit responsible for progression is a random event, not cumulative damage.Once the clonal plasma cell population is created and progresses to MM, patients develop symptoms (eg, hypercalcemia, lytic bone lesions, renal dysfunction, and anemia) related to the infiltration of plasma cells into the bone or other organs or to kidney damage from excess light chains.

6. PATHOLOGIC FEATURES

A.Monoclonal proteins : The vast majority (97 percent) of patients with MM will have a monoclonal (M) protein produced and secreted by the malignant plasma cells, which can be detected by protein electrophoresis of the serum (SPEP) and/or of an aliquot of urine (UPEP) from a 24-hour collection combined with immunofixation of the serum and urine [20]. The M-protein usually presents as a single narrow peak, like a church spire, in the gamma, beta, or alpha-2 region of the densitometer tracing (figure 3).Serum immunofixation confirms the presence of an M-protein and determines its type. The malignant plasma cells can produce immunoglobulin heavy chains plus light chains, light chains alone, or neither with the following frequencies on serum immunofixation [20]:

- IgG–52percent
- IgA–21percent
- Kappaorlambdalightchainonly(BenceJones)–16percent.
- IgD–2percent
- Biclonal–2percent
- IgM–0.5percent

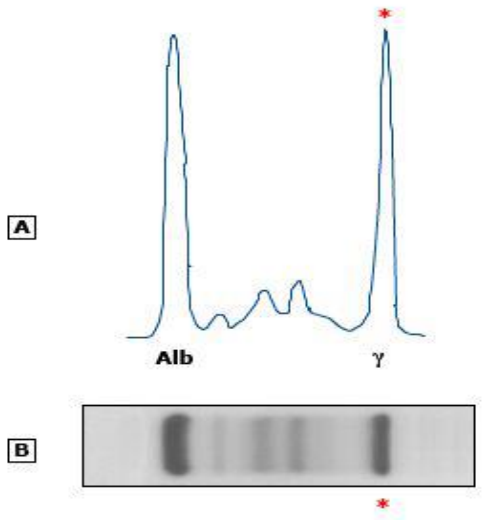


Figure 3 :(A) Densitometer tracing of these findings reveals a tall, narrow-based peak (red asterisk) of gamma mobility(B) A dense, localized band (red asterisk) representing a monoclonal protein of gamma mobility is seen on serum protein electrophoresis.

B.Light chain myeloma : Up to 20 percent of myeloma is characterized by only a light chain in the serum or urine, lacking expression of the immunoglobulin heavy chain. These patients are detected readily by serum free light chain (FLC) and UPEP and urine immunofixation. The incidence of renal failure is much higher in light chain myeloma, as the serum creatinine is ≥2 mg/dL (177 micromol/L) in approximately one-third of these patients at presentation.

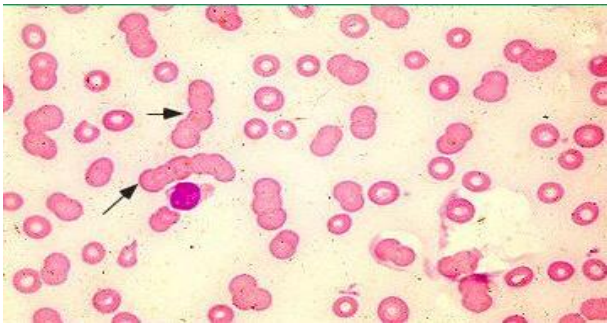
C.Nonsecretory myeloma : Approximately 3 percent of patients with MM have no M-protein in the serum or urine on immunofixation at the time of diagnosis [20]. In approximately 60 percent of patients with myeloma who have a normal serum and urine immunofixation, monoclonal FLC can be detected in the serum using FLC assays [21-22]. The FLC assay measures serum kappa and lambda light chain levels, which can then be expressed as a FLC kappa to lambda ratio. Patients without proliferative disorders of plasma cells or B-lymphocytes have normal FLC ratios. Patients with myeloma who have normal serum and urine immunofixation as well as a normal serum FLC ratio are considered to have true nonsecretory myeloma [23]. Of these, the majority (approximately 85 percent) will have M-protein that can be detected in the cytoplasm of the neoplastic plasma cells by immunochemistry, but have impaired secretion of this protein.

D.Oligo- secretory myeloma: Approximately 5 to 10 percent of patients with MM have oligo- secretory myeloma at diagnosis, defined as absence of measurable disease in serum or urine by the following parameters:

● SerumM-protein<1g/dL,and

● UrineM-protein<200mg/24hours

E.Peripheral smear: The most frequent findings on peripheral smear are rouleaux formation (>50 percent), leukopenia (20 percent), and thrombocytopenia (5 percent) . Rouleaux formation is the phenomenon when red cells take on the appearance of a stack of coins in diluted suspensions of blood and is seen in patients with elevated serum protein levels (picture 1).



Picture 1: Rouleaux formation in peripheral blood smear in patient with multiple myeloma.

7. CLINICAL PRESENTATION

Most patients with MM present with signs or symptoms related to the infiltration of plasma cells into the bone or other organs or to kidney damage from excess light chains:

● Anemia : A normocytic, normochromic anemia (hemoglobin ≤12 g/dL) is present in 73 percent at diagnosis and in 97 percent at some time during the course of the disease and macrocytosis (mean corpuscular volume [MCV] >100 fL) was present in 9 percent .This anemia can be related to bone marrow replacement, kidney damage, and/or can be due to dilution in the case of a large M-protein. Anemia commonly results in complaints of fatigue and pallor seen on physical examination.

● Bone pain: particularly in the back or chest, and less often in the extremities, is present at the time of diagnosis in approximately 60 percent of patients. Plasmacytomas of the ribs occur and can present either as expanding costal lesions or soft tissue masses.

● Elevated creatinine : Two major causes of renal insufficiency in patients with MM are light chain cast nephropathy (also called myeloma kidney) and hypercalcemia. The serum creatinine concentration is increased in almost one-half of patients at diagnosis (and is >2 mg/dL [177 micromol/L] in approximately 20 percent); renal failure may be the presenting manifestation of MM. Other causes of renal failure in a patient with MM include concurrent light chain (AL) amyloidosis, light chain deposition disease, and drug-induced renal damage.

● Hypercalcemia : Hypercalcemia is found in 28 percent of one series of patients with MM at the time of diagnosis; serum calcium was ≥11 mg/dL (2.75 mmol/liter) in 13 percent and can require emergent treatment .

● Neurologic disease : the most common neurologic complication of MM is radiculopathy and usually affect the thoracic or lumbosacral area, is It can result from compression of the nerve by a paravertebral plasmacytoma or rarely by the collapsed bone itself.

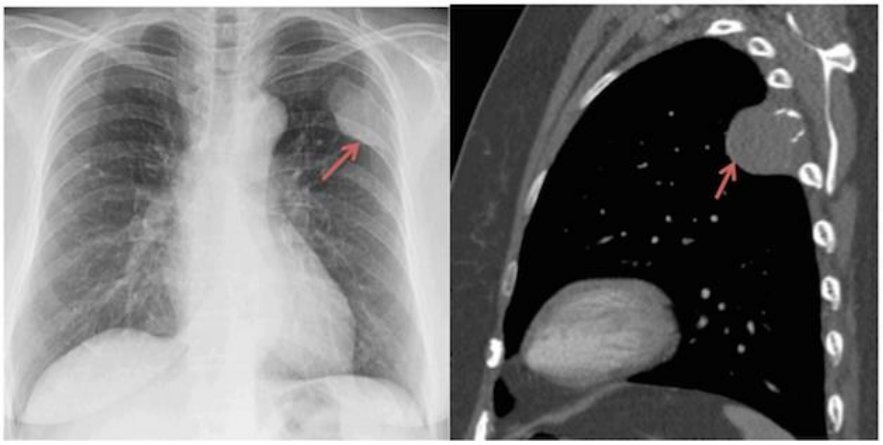
● Cord compression–Spinal cord compression from an extramedullary plasmacytoma or a bone fragment due to fracture of a vertebral body occurs in approximately 5 percent of patients; it should be suspected in patients presenting with severe back pain along with weakness or paresthesias of the lower extremities, or bladder or bowel dysfunction or incontinence.This set of symptoms constitutes a medical emergency; magnetic resonance imaging (MRI) or computed tomographic myelography of the entire spine must be performed immediately, with appropriate follow-up treatment by chemotherapy, radiotherapy, or neurosurgery to avoid permanent paraplegia.

● Central nervous system(CNS)involvement : Intracranial plasmacytomas are rare and almost always represent extensions of myelomatous lesions of the skull or plasmacytomas involving the clivus or base of the skull.

● Symptoms and signs present in 5 percent or less included: paresthesias (5 percent), hepatomegaly (4 percent), splenomegaly (1 percent), lymphadenopathy (1 percent), and fever (0.7 percent). Pleural effusion and diffuse pulmonary involvement due to plasma cell infiltration are rare and usually occur in advanced disease.

●Extramedullary plasmacytomas (EP) : are seen in approximately 7 percent of patients with MM at the time of diagnosis (Picture 2)and are best diagnosed by positron emission tomography/computed tomography (PET/CT) scan; the presence of EP at diagnosis is associated with inferior survival.

●Infection :Patients with MM are at increased risk for infection due to a combination of impaired lymphocyte function, suppression of normal plasma cell function, and hypogammaglobulinemia. Streptococcus pneumoniae and gram-negative organisms are the most frequent pathogens.



Picture 2: Extramedullary plasmacytoma .

8. DIAGNOSIS AND STAGING

Patients suspected of having MM should initially undergo a complete history and physical examination. Including specific attention to complaints of bone pain, constitutional symptoms, neurologic symptoms, and infections with detailed neurologic exam. In addition , the following laboratory studies should be performed as an initial screen to look for MM [24-25]:

● A complete blood count and differential with examination of the peripheral blood smear.

● A chemistry screen includes measurements of serum calcium,creatinine,albumin,lactate dehydrogenase, beta-2 microglobulin, and C-reactive protein.

● Serum free monoclonal light chain (FLC) analysis.

● Serum protein electrophoresis (SPEP) with immunofixation and quantitation of immunoglobulins.

● Urine analysis and 24-hour urine collection for electrophoresis (UPEP) and immunofixation.

● Serum viscosity should be measured if the M-protein concentration is high (ie,>5g/dL) .

● Bone marrow aspiration and biopsy with immunophenotyping, conventional cytogenetics ,and fluorescence in situ hybridization (FISH).

● Cross-sectional imaging is preferred over plain radiographs for the detection of bone involvement in patients being evaluated for suspected MM.

The criteria for diagnosis of MM were updated in 2014 by the International Myeloma Working Group (IMWG):

Diagnosis requires more than or equal to 10% clonal BM plasma cells or biopsy- proven bony or extra-medullary plasmacytoma and any of the following myeloma-defining events :

- Evidence of end-organ damage (the so-called CRAB criteria: hypercalcaemia, renal insufficiency, anaemia or bone lesions) that is felt to be related to the underlying plasma cell disorder. Of note, renal insufficiency can be defined not only by creatinine > 2 mg/dL but also by creatinine clearance < 40 mL/min [meas- ured by validated equations such as the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] . Moreover, lytic lesions can also be defined by CT and not only by conventional X-ray.

- Any biomarkers of malignancy:

  - ≥ 60 % clonal BM plasma cells

  -Involved/uninvolved serum FLC ratio ≥ 100

  - > 1 focal lesion on MRI studies (each focal lesion must be ≥ 5 mm in size).

Monoclonal gammopathy of undetermined significance : Monoclonal gammopathy of undetermined significance (MGUS) is diagnosed in persons who meet the following three criteria :

● Serum M-protein (IgA, IgG, or IgM)<3g/dL

● Clonal bone marrow plasma cells <10percent

● Absence of lytic lesions, anemia, hypercalcemia, andrenal insufficiency (end-organdamage) that can be attributed to the plasma cell proliferative disorder

Smoldering multiple myeloma — Smoldering multiple myeloma (SMM) is defined as:

● M-protein ≥3g/dL and /or 10 to 60 percent bone marrow plasma cells , plus

● No end-organ damage or other myeloma-defining events , and amyloidosis

International Staging System (ISS) : An ISS was developed based on 10,750 previously untreated patients with myeloma from over 17 institutions worldwide. It incorporates data on the levels of serum beta-2 microglobulin (B2M) and serum albumin to divide disease burden into three stages with prognostic significance :

● StageI–B2M<3.5mg/L and serum albumin ≥3.5g/dL.

● StageII–neither stageI nor stageIII

● StageIII–B2M≥5.5mg/L

9. TREATMENT

Treatment should be initiated in all patients with MM according to the updated definition proposed by the IMWG in 2014

Elderly patients (non-transplant setting) : The two following options are recommended based on data from randomised phase III trials , bortezomib (administered subcutaneously)/melphalan/prednisone (VMP) or lenalidomide plus low-dose dexamethasone (Rd) ; both VMP and Rd are approved in this setting by the European Medicines Agency (EMA). Rd is approved until progression of the disease. Melphalan/prednisone/thalidomide (MPT) is also approved by the EMA, but is inferior to Rd in terms of progression-free survival (PFS) and overall survival (OS). Bortezomib- cyclophosphamide and dexamethasone (VCD) is not EMA- approved (no controlled data), but is widely used and induces high response rates and prolonged PFS .Rd has recently been compared prospectively with Rd plus bortezomib (VRd), and the addition of bortezomib resulted in significantly improved PFS and OS and had an acceptable risk–benefit pro- file . Nevertheless, this triplet combination is not yet approved by the EMA. Bendamustine plus prednisone is also approved by the EMA in patients who have clinical neuropathy at time of diagnosis, precluding the use of thalidomide accord- ing to the MPT regimen or bortezomib according to the VMP regimen. Melphalan/prednisone/lenalidomide (MPR) has been evaluated in two prospective randomised studies versus melphalan and prednisone (MP) and versus MPT . but MPR was not superior

to the other combinations with a fixed number of cycles . This triplet combination is approved by the EMA but is not routinely used and cannot be considered as a standard of care. Cyclophosphamide/thalidomide/dexamethasone (CTD) has also been compared with MP and is superior in terms of response rates, but does not induce a clear survival advantage over MP.[26-27]

Younger patients (<65 years or fit patients <70 years in good clinical condition) : For patients in good clinical condition (e.g. fit patients), induction followed by high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard treatment . Two recent phase III trials comparing front-line ASCT versus ASCT at the time of first relapse showed that PFS was improved in the front-line ASCT arm (in the con- text of triplet novel agent-based induction) [27].Response rates to induction therapy have been significantly increased by the use of novel agent-based combinations. Bortezomib- dexamethasone, which is superior to the classical VAD regimen (vincristine, doxorubicin and high-dose dexamethasone) ,has become the backbone of induction therapy before ASCT .The addition of a third agent to bortezomib- dexamethasone, e.g. thalidomide (VTD), doxorubicin (PAD), lenalidomide (RVD) or cyclophosphamide (VCD), has shown higher response rates in phase II trials . Three prospective studies have already shown that VTD is superior to thalidomide- dexamethasone (TD) or bortezomib-dexamethasone .

10. CONCLUSION

MM is a plasma cell disorder with an uncontrolled expansion of clonal plasma cells associated with end-organ damage (CRAB). It is preceded by MGUS and/or smoldering myeloma. The international staging system and cytogenetics are used to risk stratify patients. Major advances have occurred over the past few years, especially with the use of IMiDs and proteasome inhibitors. Younger patients can now enjoy a median survival of 7 years (with induction therapy, preferably bortezomib-based, followed by ASCT). Older patients also have longer survivals with MPT/MPV/MPR. Maintenance therapy seems to prolong survival further but more data on long-term safety (especially with regards to SPM) is needed. Supportive care is essential and includes the prevention and treatment of complications related to the disease and its therapy.

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