

INTRODUCTION

“3 Cases of MM”

If you already know what MM is, you might still want to read on because I will be discussing an interesting dilemma that we as hematologists face today when treating patients with MM. If you don't know what MM is, you obviously must read on so that you will understand your doctors a little better when you next meet them. Multiple myeloma is a blood or hematological cancer. In Latin, “myelo” means bone marrow (BM), and “oma” means tumor or cancer. Hence, “myeloma” is a bone marrow cancer. In our bodies, the BM is found inside our bones. As you know, our skeleton is made up of many bones but not all the bones contain marrow. By and large, BM is found inside the larger bones. Moreover, when we are younger, more of the skeleton contains active marrow; but as we age, some of the BM “dries up,” as it were, and some of the bones that originally contained marrow now become devoid of it. Multiple myeloma is called “multiple” because it is often found in many separate sites in the BM of our skeleton at the time of diagnosis. The cancerous myeloma cell is a malignant plasma cell. The normal counterparts of this cell, i.e. normal plasma cells, are cells of the immune system that produce antibodies (Ab), also known as immunoglobulins (Ig), in our bodies. Antibodies protect us from invasion by foreign agents, e.g. germs. One plasma cell (of the immune system) will produce only one type of Ab. This is the concept of monoclonality. However, during an infection,

e.g. influenza, many plasma cells are activated and together they produce numerous different types of Igs that fight the flu virus. Such a concerted Ab response by many normal plasma cells is also called a polyclonal Ab response.

The situation is different in MM where only one plasma cell had at the outset become cancerous. Over time this cancerous cell multiplied itself through numerous cell divisions and gave rise to many copies or clones of itself. Each member of this clone of malignant plasma cells produces the same Ab or Ig (e.g. Ig class G or IgG). Ultimately, the Abs that are secreted by this clone of MM cells are identical and are called monoclonal Abs (mAbs). In the context of MM, these mAbs are also called monoclonal proteins or myeloma proteins or M-proteins. Because MM cells arise in the BM, normal blood production and blood counts may be affected by the presence of the cancer, i.e. suppressed (e.g. patients may have anemia). Hence, in established MM, patients often complain of fatigue and poor immunity. Moreover, because the BM is found inside the bones of the skeleton, patients with MM also frequently complain of bone pain and high blood calcium levels (hypercalcemia) because of bone destruction, i.e. MM bone disease. Furthermore, because the smaller component parts of the Ig molecule (also called the light chains) are able to pass through the filtering system of the kidneys (the glomeruli), and are capable of inducing toxic reactions in the tubes of the kidneys (the renal tubules), M-protein light chains can lead to varying degrees of kidney (renal) failure. In summary, hypercalcemia, renal failure, anemia and bone pain/disease, which form the acronym “CRAB,” are the clinical hallmarks of MM. In the presence of at least some of the clinical features outlined by “CRAB,” the diagnosis of MM is confirmed by the biochemical identification of the M-protein and the presence of malignant plasma cells in the BM sample.

Case 1. A Typical MM Patient

At about 3:00 p.m. on a hot and humid afternoon, a 45-year-old lorry driver was having a late lunch at work when he suddenly lost

his balance and fell from his chair and onto the floor, hitting his head on the floor in the process. He had apparently fractured his right hip and was writhing in pain, almost to the point of delirium. The cause of the injury was trivial — he had reached forward and towards his right to pick up his newspapers to read when the upper part of his right leg snapped into two. This was quite evident on the X-rays that were subsequently taken at the Accident and Emergency department.

Further X-rays demonstrated multiple small spherical lesions in the hip and leg bones, as well as in the skull, that resembled bones that had been moth-eaten. These multiple bone tumors, called lytic lesions,^c were typical findings of MM bone disease. Indeed, the whole skeleton could be riddled by these lytic lesions, thus making the bones very brittle. At the slightest injury, these bones could simply fracture — so-called pathological fractures. Because the fracture site does not contain bone or bone cells, but rather cancer cells, bone healing is frequently slow or impossible, and bone pain intractable. Indeed, MM is one of the most painful cancers that we know of. Through other laboratory tests, it was subsequently found that this patient had hypercalcemia, anemia and renal impairment, all the hallmarks of MM. Biochemical tests also confirmed the presence of the M-protein, which was of the subtype IgG κ ^d (for immunoglobulin G and the kappa light chain (LC) subtype). He went on to receive standard therapy for MM and died two-and-a-half years later.

Case 2. A Less Obvious Case of MM

A frail 94-year-old woman was being nursed in the Medical Intensive Care Unit (ICU) of a local hospital. She was a domestic helper in

^c In Latin, the term for bone is “osteo-”. Thinning of bone is also known as osteopenia. When bone thinning is marked in a certain area, that lesion is called an osteolytic lesion. By contrast, in some diseases bone formation is increased in certain areas. This kind of lesion is called an osteoblastic lesion.

^d The common subtypes of MM are IgG and IgA; with either kappa or lambda light chains. For example IgG κ , IgG λ , IgA κ or IgA λ .

her youth, and a relatively petit and quiet woman who rarely complained about any sickness. A fall whilst walking in the rain a fortnight ago had changed her life completely. She had been unconscious ever since. A hairline fracture at the back of her skull and multiple broken ribs were detected by X-rays. After three days in hospital, she developed a fearsome fever due to widespread pneumonia in both lungs. Despite the use of antibiotics, her condition continued to deteriorate and decompensate.

She was nursed in the Medical ICU because of a dangerously low blood pressure, so low that augmentation using continuous intravenous medication (called inotropes) had to be instituted. Moreover, she required repeated blood transfusions for persistent anemia. Serial chest X-rays performed to monitor her pneumonia revealed that some of the rib fractures were actually old fractures that had most likely preceded her fall by a number of months. To the trained eye, some degree of bone healing had already taken place in these fractures. In other words, she already had rib fractures that she didn't even know of, again typical of pathological fractures. A very mild hypercalcemia and mild renal impairment alerted her doctors to the possibility that she could have MM. The appropriate investigations were performed and these confirmed that she indeed had an IgG κ MM.

Because she was very sick, it was decided that treatment would be attenuated (individualized). An extremely gentle regimen comprising 5 mg of prednisolone (Pred, a steroid or glucocorticoid) once a day was selected for her MM. After just four days of therapy, her fever settled and she regained consciousness. After another two weeks of treatment, she was discharged from hospital and returned home in a wheelchair. This patient continued to be given higher daily doses of Pred for several more months but she finally succumbed to her MM. Her treatment was individualized and palliative (i.e. not curative and not for prolonging survival), the aim being to give her the best quality of life (QoL) possible.

Case 3. Does this Patient have MM?

The next patient is one of the most difficult MM cases that I have ever diagnosed. I wonder till today if the delay in diagnosis has had made a difference to the outcome of his treatment. This is a 60-year-old man, who has worked for many years as a welder before he was admitted to a local hospital for severe backache. Apparently, he was otherwise a relatively fit chap, and was watching television when he developed an acute and severe backache. He described himself as being hit in the lower back by a torpedo and had become immediately incapacitated by excruciating pain. He couldn't even turn about in bed or bathe himself.

As expected, he was admitted under the Orthopedic Service, and underwent magnetic resonance imaging (MRI) scanning within hours of admission. The MRI scan was completely normal. Moreover, a radionuclide bone scan was also negative and no further orthopedic intervention was performed. He was then transferred to the Neurology Service for further testing. A whole barrage of tests was done, including lumbar puncture (LP), but all these tests were again negative. Pain continued to be severe and was relieved only by high doses of opiate-based medicines like morphine. As a result, he developed severe nausea and vomiting, ileus (paralysis of the gut) and constipation and was referred to the Gastroenterology Service. Yet again, further tests were carried out, including computerized tomographic (CT) scans, gastroscopy and colonoscopy. Again no abnormalities of the abdominal organs were detected. It was not difficult to understand his frustration.

“My pain is so bad,” he said, “I cannot sleep. I take so much morphine; I'm worried I will be addicted. So I ask for sleeping pills. But the doctors say I can also be addicted to sleeping pills and cannot take too many of those. I vomit or cannot pass motion every time I take morphine. I really feel like dying.”

All his routine blood and urine tests were normal except for borderline hypercalcemia and increased Igs. He was then suspected to have MM and I was called to review him. Unfortunately, all the specific MM studies, BM studies and full skeletal survey were also

negative. The Ig fraction was in fact polyclonal^e and a good healthy BM was found when examined. To all intents and purposes, MM could be ruled out. But my suspicions of MM continued to be high, and I then asked for a bone mineral density (BMD) dual-energy X-ray absorptiometry (DXA or DEXA) scan to be done. This showed severe osteopenia with bone thinning well below three standard deviations (SDs), supporting the presence of diffuse MM bone disease. Parathyroid hormone levels were depressed and the CT scan of the neck was negative for parathyroid adenomas, excluding a more typical cause of severe and painful diffuse bone disease.

Whilst we were all puzzled by the data before us, the patient suffered a second attack of acute pain in the right seventh rib. An MRI now confirmed the presence of an expansile lesion in the posterior part of the rib. A rib resection (partial removal of the diseased rib) was immediately performed and the histology revealed a plasmacytoma (plasma cell tumor)^f with no Ig heavy chain (IgH) or Ig LC secretion, i.e. it was a non-secretory plasma cell tumor. Further MRI scans and a second BM examination were yet again negative. It was difficult to make the diagnosis because the diagnostic criteria were not fulfilled. However, even though the only known lesion, the cancerous rib was removed, he continued to have extremely severe symptoms, and not treating him would simply be inhumane.

I therefore made the final decision to treat him as a very non-typical (atypical) case of MM. I decided to individualize his treatment and to avoid chemotherapy for as long as it was possible. A non-cytotoxic (i.e. targeted therapies) regimen was commenced and within three hours his pain subsided. And in two days, he was

^e The globulin or Ig fraction in MM is typically monoclonal (i.e. M-protein or M-band). In inflammatory or reactive processes, e.g. infections, a polyclonal Ig fraction may be found.

^f Multiple myeloma cells are cancerous plasma cells. A plasma cell tumor or plasmacytoma can exist as a single lesion or as multiple lesions. When present as a single lesion, it is called a solitary plasmacytoma; and when present as multiple lesions, the diagnosis is MM.

pain-free! After six months of therapy (two months in and out of hospital, and four months as an outpatient), he was in total clinical remission and able to perform all his daily activities. The osteopenia and high polyclonal Igs had both resolved. Interestingly, the initial Hb of 18.0 g/dL (high normal) had decreased to about 13.0 g/dL after treatment. Repeated BM examinations continued to be negative for MM. Today, he remains well after completing eight cycles of targeted therapies that are specific for MM. Could MM be a collection of more diseases than one?