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Case report 1

Priapism and pyrexia of unknown origin presenting as a relapse of multiple myeloma

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Abstract

Pyrexia of unknown origin (PUO) is defined as a body temperature >38.3°C on several occasions for >3 weeks with failure of diagnosis despite one week of inpatient investigations or three outpatient visits. Aetiology for PUO may be infective, inflammatory, autoimmune, malignant, miscellaneous or remains undiagnosed. We describe a patient diagnosed with multiple myeloma (ISS-stage II) who completed induction chemotherapy and presented with PUO and extensive thrombosis as a complication of relapsed myeloma (very rare; 0.2% in myeloma). A 62-year-old man, with diagnosed multiple myeloma, achieved a very good partial remission after 6 cycles of bortezomib-thalidomide-dexamethasone regimen, presented with PUO and right lower limb deep vein thrombosis. His thrombosis was managed successfully with anticoagulation. While on therapeutic anticoagulation with warfarin and being investigated extensively for PUO without a focus, he developed priapism due to bilateral internal pudendal vein thrombosis. His anticoagulation was intensified to a target INR of 2.5-3.5. He recovered without residual damage. Despite broad spectrum antimicrobial agents, trial of antimalarial and anti-tuberculosis treatment, he remained pyrexial with rising inflammatory markers (ESR, CRP). Relapsed multiple myeloma was confirmed with 30% bone marrow plasma cells and raised serum monoclonal paraprotein levels of 23.78g/L. He was restarted on chemotherapy with bortezomib-lenalidomide-dexa-methasone. His PUO of two months subsided with one week of chemotherapy.

This case illustrates an atypical presentation of relapsed myeloma and highlights the importance of achieving early diagnosis with a systematic approach and making optimum treatment choice after careful evaluation of previous treatment, drug toxicities, patient's condition and available treatment options.

Introduction

Cancers constitute approximately 2-25% of cases of PUO. Pyrogenic cytokine production or spontaneous tumour necrosis (with or without secondary infection) is the likely basis of most cancer related fever. Neoplasms most commonly associated with PUO with high spiking fever are renal cell carcinoma, lymphoma, hepatocellular, ovarian cancer, atrial myxoma, Castleman's disease.

During the course of multiple myeloma, PUO is very rare, accounting for 0.2%. Differential diagnostic possibilities are infections, secondary/superimposed malignancies, plasma cell leukaemia or relapse of multiple myeloma. PUO due to infection in multiple myeloma is a result of overproduction of monoclonal, non-functional paraprotein and suppression of polyclonal B lymphocytes by malignant plasma cells. PUO due to disease activity is exceedingly rare and it can occur due to pyrexial cytokine production and the fever completely disappears with successful chemotherapy.

Case report

Our patient is a 62-year-old previously healthy male who initially presented with bilateral hip pain for more than three months duration to an

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orthopaedic unit. X rays revealed bilateral pathological fractures of the neck of femur. Contrast enhanced computerized tomography confirmed lytic lesions over iliac bones, throughout the spine and non-displaced rib fractures with multiple ribs involved and bilateral pathological fracture necks of femur. He also had moderate anaemia with haemoglobin of 8.8g/dL and ESR of 120 mm first hour. The bone marrow biopsy showed 45% clonal plasma cells. His initial paraprotein level was 55.5 g/L and the serum immunofixation confirmed IgG kappa myeloma with initial ISS stage-III.

His initial (albumin corrected) serum calcium level was-2.19 mg/dL, serum creatinine 125µmol/L, serum albumin 26.5g/L, beta2 microglobulin level 5.6 mg/L and lactate dehydrogenase level (LDH) 306.3 units/L.

Bilateral dynamic hip screws (DHF) were inserted for neck of femur fractures. The patient was started bortezomib, thalidomide and dexamethasone (VTD) 28-day cycles. He was given subcutaneous enoxaparin 40 mg daily as thromboprophylaxis for three cycles of VTD until fully mobilized. He completed 6 cycles of VTD with a very good partial remission (VGPR) with serum paraprotein level of 3.2g/L at the end of 6th cycle.

One month after completing chemotherapy, he presented with right sided lower limb swelling and pain associated with high fever spikes for two weeks duration. He was admitted for further evaluation.

On examination, he had tachycardia and high fever with a blood pressure of 110/70 mmHg. There was no lymphadenopathy. His right lower limb had swelling, redness and mild tenderness, but dorsalis pedis pulsation was present. His respiratory, cardiovascular, abdominal and nervous system examination were unremarkable. He was started on oral clindamycin 500 mg twice daily for cellulitis. Duplex scan of bilateral lower limbs revealed a right sided thrombosis from external iliac vein, common femoral vein up to popliteal vein. He was started on anticoagulation initially with subcutaneous enoxaparin 1mg/kg twice a day and warfarin. Enoxaparin was continued until INR reaches 2-3 range.

With antibiotics cellulitis subsided but the fever continued. He was extensively investigated for PUO. He had intermittent high-grade fever with temperature up to 103°F. It was associated with significant weight loss and loss of appetite despite absence of respiratory, cardiac, abdominal or neurological involvement. Ultra sound scan of abdomen did not reveal any lymphadenopathy or organomegaly. He had no contact history of tuberculosis. He gave a history of severe falciparum malaria needing intensive care one year back when he was in Ruvanda.

His FBC revealed WBC-15.41×10^9/L (N- 61% L-29.1%), moderate anaemia (haemoglobin 7.2 g/dL, MCV 86.9fL, MCH 32.1pg, MCHC 34.9g/dL) and thrombocytosis (platelet 635×10^9/L). Blood picture showed moderate anaemia with red cell changes due to anaemia of chronic disease, B12 deficiency +/- iron deficiency anaemia. White cell changes with marked rouleaux formation were suggestive of ongoing bacterial infection + inflammatory/ neoplastic process. Reticulocyte count was normal (2%). Activated partial clotting time was normal with plasma fibrinogen 4.2 g/L. LDH was slightly elevated (417 IU/L). Direct antiglobulin test was negative.

He had elevated inflammatory markers (ESR - 138mm/1st hour, CRP-320 mg/L). Procalcitonin levels showed a rising trend (26, 56, 158 ng/mL).

His liver function tests were normal throughout this period (AST 18 U/L, ALT 17 U/L, bilirubin; total 9.65umol/L, direct 3.32umol/L indirect 6.3umol/L, total protein 75.2g/L, albumin 25.1g/L, globulin 49.13g/L, gamma glutamyl transferase 122.6U/L, alkaline phosphatase 109U/L). Renal function test was normal (serum creatinine 80.7umol/L) with normal serum electrolytes. (serum sodium 136mmol/L; serum potassium 4 mmol/L, albumin corrected Ca^{2+} 2.24 mmol/L).

His chest radiography and abdominal ultrasonography showed no focus of infection. Electro-

cardiogram was normal and troponin I was negative. Both transthoracic and transoesophageal echocardiograms excluded vegetations suggestive of infective endocarditis. Antinuclear antibody was negative.

On day 10 of hospital stay, while on warfarin with therapeutic INR, the patient developed priapism due to bilateral internal pudendal vein thrombosis. Warfarin was withheld and unfractionated heparin (UFH) was started. The genitourinary team attended immediately for the management of priapism and he recovered without any residual effect. After 3 days of UFH he was reverted to LMWH and warfarin targeting higher therapeutic rage of INR (2.5 -3.5). We arranged urgent CECT neck to pelvis to exclude other secondary malignancies. It revealed, partial recanalization of thrombus in inferior vena cava, right common iliac vein and bilateral external iliac veins, multiple lytic lesions involving almost all vertebras, left ala of sacrum, left ilium and left T9 and T10 ribs. No other malignant lesions were detected and evidence of bilateral DHS seen. Sickling test was negative.

While being investigated for prolonged fever, he developed severe shortness of breath with saturation dropping to 80% on normal air. CTPA excluded pulmonary embolism. His arterial blood gas analysis showed low potassium and bicarbonate levels and metabolic acidosis with partial compensated respiratory alkalosis, indicating the possibility of renal tubular loss of electrolytes that can occur with multiple myeloma. He recovered with oral electrolyte replacement therapy.

His PUO remained undiagnosed despite numerous investigations including repeatedly negative results obtained for blood cultures for both bacteria and fungi, urine cultures, malarial thin and thick films with malarial antigen test which was done thrice, viral serological tests, mantoux test and sputum acid fast bacilli, melioidosis antibodies, brucellosis antibody, galactomannan antigen, toxoplasma antibodies, covid antigen + antibody and HIV-1 and 2 serology. He had persistently high ESR (> 100 mm/1st hour), CRP and procalcitonin levels.

With a history of malaria, He was given anti-malarials (chloroquine for 3 days) even blood investigations did not give positive clues, with no response. He was treated with several intravenous antibiotics, including meropenem, piperacillin-tazobactum, imipenem in sequence with no response.

As his ESR remained high, a sample for serum protein electrophoresis was requested which indicated an early biochemical relapse 23.78 g/L. Repeat bone marrow examination revealed 30% abnormal plasma cells confirming relapse of plasma cell myeloma.

Meanwhile, anti-tuberculosis treatment was commenced even without proven evidence of the disease, but he remained pyrexial even after two weeks of anti TB therapy. As his procalcitonin and CRP remained elevated, we delayed anti-myeloma treatment for a further two weeks and continued antibiotics with anti-tuberculosis treatment.

When his serum procalcitonin level was gradually reduced to 3.45 ng/mL, despite elevated CRP, he was started bortezomib, lenalidomide, and dexamethasone (VRD) 21day cycles on Day 42 of hospital stay while on anti-tuberculosis therapy. He became fever free, on day 7 after starting anti-myeloma treatment and got discharged after 56 days of hospital stay. He had residual effect of renal salt wasting of potassium and bicarbonate which was managed with oral salt replacement therapy. He continued on anti-myeloma therapy for early relapsed myeloma, warfarin with higher INR target for extensive thrombosis, anti-tuberculosis treatment which was for a total of 6 months period and electrolytes replacement with regular monitoring. After first cycle of chemotherapy his paraprotein level dropped to 11g/L indicating response.

Discussion

PUO is not a biologically uniform phenomenon but rather a common manifestation of multiple disease processes. The approach should be individualized based on a specific clinical scenario.

Detailed history and physical examination, with careful attention to skin, joints, lymph nodes, medication history, travel, dietary and animal exposure is very important in initial evaluation of PUO. Investigations should be from basic to advanced according to clinical relevance. Management is often with empirically administering antimicrobial or anti-inflammatory therapy in a patient with protracted fever. However, if the patient has neutropenia, severely immunocompromised or has a rapidly deteriorating clinical state every attempt should be made to establish the diagnosis first. "The naproxen challenge" has been proposed to differentiate PUO due to cancer from PUO due to infection. Although clinicians may choose to use naproxen for symptomatic relief of fevers, amelioration or resolution of fevers with naproxen does not obviate the need for a rigorous evaluation of infection.

Venous thromboembolism (VTE) is significantly increased in malignancies. Among haematological malignancies, multiple myeloma confers an especially high risk, with at least 10% of patients developing VTE during their disease history, causing substantial morbidity and mortality. The thrombogenicity of myeloma is multifactorial including

Disease related

- Immunoglobulin dependent;
  - hyperviscosity
  - defective fibrin polymerization and fibrinolysis,
  - lupus anticoagulant activity of the paraprotein, antibodies against protein C and S, acquired APC resistance.
- Immunoglobulin independent;
  - elevated PAI-I,
  - increased IL 6, VEGF,
  - elevated FVIII, VWF and fibrinogen levels,
  - increased cell surface phosphatidylserine expression,
  - increased endothelial tissue factor expression,
  - acquired APC resistance due to reduced level of thrombomodulin.

Treatment related

- Thalidomide, lenalidomide, dexamethasone, multi agent chemotherapy, proteasome inhibitor-carfilzomib, erythropoietin stimulating agents, indwelling central catheters.

Patient related factors

- Severe infection, fractures and other causes of immobility, elevated body mass index, comorbidities (renal failure, autoimmune disease, cardiac disease, diabetes mellitus), surgery, anaesthesia, trauma, history of VTE or inherited thrombophilia.

Despite routine use of thromboprophylaxis, these patients can still develop VTE, like in our patient. Therefore, appropriate identification of risk factors of VTE and subsequent stratification of patients is of paramount importance in the optimal care of a patient with myeloma.

Currently there is a pragmatic approach, to manage a patient who requires pharmacological thromboprophylaxis, taking into consideration the risk factors as proposed by the IMWG model;

- low risk; patients treated with thalidomide or lenalidomide with no or one risk factor.
- high risk; patients treated with thalidomide or lenalidomide with two or more risk factors.
- those receiving high dose dexamethasone, doxorubicin or multi-agent chemotherapy irrespective of preceding risk factors.
- very high risk; patients who have had previous thrombosis
- those known to have antithrombin deficiency

Asprin/prophylactic LMWH is indicated for low-risk patients. Prophylactic LMWH/ warfarin (target INR

2-3) is indicated for high-risk patients and therapeutic dose of LMWH or high prophylaxis LMWH (with anti Xa level of 0.4 IU/mL) for very high-risk patients. Direct oral anticoagulants (DOACS) for low and high-risk patients may be chosen in clinical trials or according to patient's wishes after appropriate counselling, although still it is unlicensed.

If there is recurrent thrombosis while on anticoagulant therapy in patients with multiple myeloma, need to check compliance and rule out other causes for thrombosis while modifying the ongoing risk factors. If patient is already on warfarin, we need to check whether INR is within target range. If it is not within range, ensure whether it achieves therapeutic range with dose adjustments. If patient is already within therapeutic range, it is advisable to switch to LMWH. If patient is on DOACS and develops a recurrence, need to measure drug levels and if it is in therapeutic range switch to LMWH or increase DOACs dose (unlicensed). If it is not in therapeutic range switch to LMWH.

If patient is on LMWH, need to measure anti Xa levels. If it is within therapeutic range, increase LMWH dose by 20-25% or give split dose therapeutic LMWH with monitoring.

In conclusion, this case highlights the importance of anticoagulation in extensive thrombosis of myeloma, searching monoclonal proteins (eg. serum protein electrophoresis/urine Bence-Jones protein) as a part of the diagnostic algorithm of PUO along with infectious disease work up and importance of including multiple myeloma in the differential diagnosis of PUO to reduce unnecessary testing, and to rapidly establish the diagnosis to initiate effective treatment.

CECT abdomen and pelvis showing thrombus in inferior vena cava (Figure 1), right common iliac vein (Figure 2) and right external iliac veins (Figure 3).

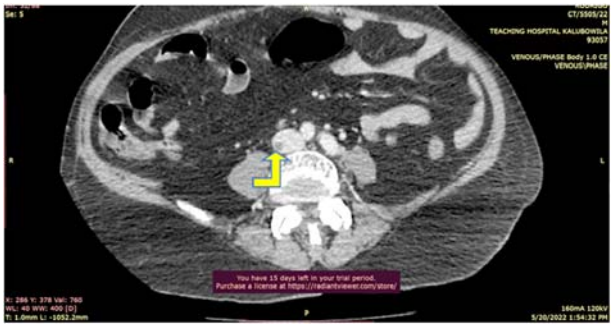

Figure 1.

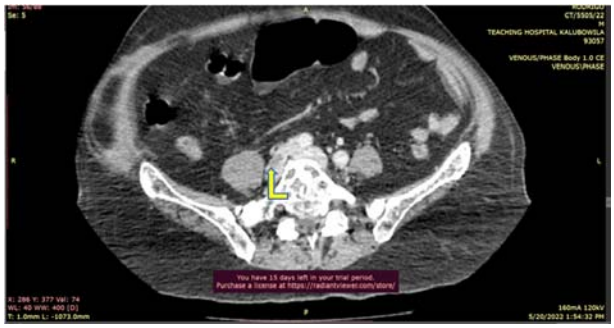

Figure 2.

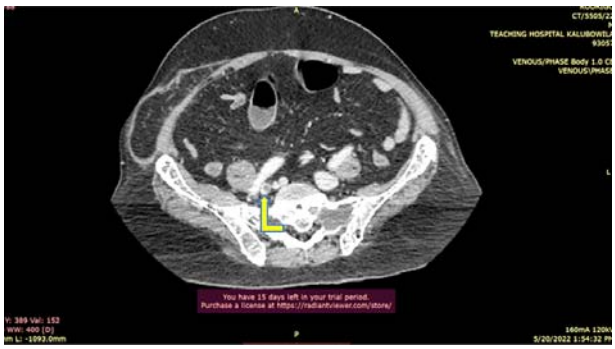

Figure 3.

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