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Case Report

Systemic vasculitis with prolonged pyrexia, recurrent facial urticaria, skin nodules, pleural effusions and venous thrombosis: an unusual presentation of an uncommon disease

Systemische Vaskulitis mit langen fieberhaften Zuständen, wiederholter Urtikaria im Gesicht, Hautknötchen, Pleuraerguss und Venenthrombose: eine ungewöhnliche Vorstellung einer seltenen Erkrankung

Abstract

Classically presenting with multiple or single peripheral cytopenias of variable severity, the myelodysplastic syndromes may occasionally present with bizarre manifestations that confuse the clinical picture and result in significant delays in making the correct diagnosis. We describe the case of an elderly male patient whose presentation with prolonged unexplained fever coupled with cutaneous, pulmonary and other systemic features of inflammation was finally diagnosed as having a primary myelodysplastic syndrome with associated vasculitis after a delay of 4 years.

Keywords: myelodysplastic syndrome, vasculitis, diagnosis

Zusammenfassung

Das klassische myelodysplastische Syndrom ist gekennzeichnet durch multiple oder vereinzelte Cytopenien verschiedener Schweregrade. Das myelodysplastische Syndrom kann bisweilen abweichende Manifestationen aufweisen, die das klinische Erscheinungsbild ungewöhnlich verändern und damit die Stellung der korrekten Diagnose wesentlich verzögern. Wir beschreiben den Fall eines älteren männlichen Patienten, der mit langandauernden, unerklärlichen Fieberzuständen zusammen mit systemischen Entzündungserscheinungen auch an der Haut und in der Lunge vorgestellt wurde. Nach 4 Jahren Verzögerung wurde die Diagnose eines primären myelodysplastischen Syndroms mit begleitender Vasculitis gestellt.

Schlüsselwörter: myelodysplastisches Syndrom, Vaskulitis, Diagnose

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Introduction

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of pre-malignant marrow stem cell disorders characterized by cellular dysplasia and ineffective erythropoieis associated with increased apoptotic cell death [1], [2]. These syndromes may arise de novo (primary) or occur years after exposure to potentially mutagenic therapy (secondary) e.g. after radiation exposure or following cytotoxic chemotherapy [1].
As well as presenting with cytopenias of various degrees (anemia, bleeding and infections), some patients with the myelodysplastic syndromes have recently been shown to develop significant rheumatic and immunological manifestations [3], [4]. We describe a middle-aged man whose primary presenting features of an underlying myelodysplastic syndrome were related to widespread vasculitis namely pyrexia of unknown origin, pneumonitis, bilateral pleural effusion, recurrent deep venous thrombosis, recurrent lobular panniculitis, facial urticaria, and epididymo-orchitis.

Case presentation

Presenting complaints

A 65 year old Caucasian male was admitted acutely complaining of generally feeling unwell with fever, painful skin swellings over his arms and legs, headache and epigastric pains.

Past history

He had a complex 4 years history when he presented with intermittent fever and chills, arthralgia of large joints, painful skin nodules of arms and legs, dry cough, shortness of breath, redness of his right eye, painful right testicle, anorexia and weight loss of two months duration. He denied oral or genital ulcers. Over the ensuing two months he was extensively investigated to define the underlying disease.

Main abnormalities

The main abnormalities on previous investigations were as follows:

1. Complete blood count: Hemoglobin 106 gram per litre, mean corpuscular volume (MCV) 97.5, erythrocyte sedimentation rate (ESR) 134 mm/Hr, C-reactive protein (CRP) 135 mg/dl (normal less than 3.5). Normal total white blood cell (WBC) count and differential. Rouleoux, oval macrocytes. Pseudo Pelger-Huet cells and occasional myelocytes on film. Platelet and reticulocyte counts were normal.
2. Liver function test: gamma-glutamyl transferase 172 (7–64 iu/l), alkaline phosphatase 399 (42–121 iu/l), albumin 16 (32–55 iu/l), bilirubin and alanine aminotransferase normal.
3. Urea 10.2 (3–6 mmol/l), creatinine137 (53–115 umol/l). Normal sodium and potassium.
4. Immunoglobulin (IG) G level was raised (polyclonal) 19.1 (8–18 gm/l). Normal IgM, IgA and IgE levels.

Radiological tests

Chest X-ray: Bilateral patchy basal consolidation and mild bilateral pleural effusions which were confirmed on computerized tomographic scans.
Ultrasound scan of scrotal sac showed changes consistent with epididymo-orchitis.
CT scan of the abdomen: normal.

Serological tests

The following serological tests were done and found to be negative: Hepatitis B & C screen, HIV test, anti-nuclear antibodies, anti-DNA antibodies, rheumatoid factor, anti-cytoplasmic antibodies, anti-cardiolipin antibodies, Coomb's test, ASO titre, cryoglobulins, Brucella serology, complement levels, C1-esterase level.

Other tests

Other negative tests done for a possible infective agent: malaria film, Brucella culture, Mantoux test, sputa for acid fast bacilli, leprosy nasal smears, urine microscopy.

Skin biopsies

Two skin biopsies were taken:

- Sample 1: Summary of findings:
  Skin showing extravasation of erythrocytes in the upper dermis. Deeper down there is a panniculitis, mainly of lobular type. The inflammation consists of histiocytic cells, lymphocytes, and granulocytes. There is a large vessel with thickened muscular wall containing granulocytes and lymphocytes. Picture of panniculitis with vasculitis.
- Sample 2: Summary of findings:
  Skin fragment shows rather normal epidermis. Upper dermis shows extravasation of erythrocytes. Capillary blood vessels show sometimes thickened walls, containing leukocytes. Picture consistent with leucocytoclastic vasculitis.

Other biopsies

Other biopsies taken and found to be negative/normal were:

- Bilateral temporal artery biopsies
- Conjuctival biopsy
- Liver biopsy
- Bronchoscopy and bronchoscopic samples

Bone marrow aspirate/biopsy: Unsuccessful initial attempt. Patient declined a repeat.

Clinical course

The patient was empirically treated with broad spectrum antibiotics, anti-malarial therapy followed by treatment for tuberculosis and brucellosis, without improvement. Treatment with oral prednisolone 60 mg a day resulted in prompt improvement in his well-being, subsidence of his fever and normalization of his ESR.
Over the subsequent years, he was maintained on prednisolone therapy. However, it became apparent that reducing his prednisolone dose or non-compliance on the patient's part resulted in the prompt recurrence of his painful nodular skin lesions, fever, arthralgia, urticarial facial swellings, lung infiltrates (pneumonitis), and increase in both C-reactive protein and ESR (above 100 mm/hr). His general condition usually worsened during these episodes, resulting in frequent hospital admissions. Unfortunately, high dose prednisolone led to the development of diabetes mellitus which necessitated using oral hypoglycemic agents. A brief trial of azathioprine as a steroid-sparing agent worsened his anemia and it was discontinued.

Bone marrow examination at another hospital showed myelodysplasia but with no cytogenetic abnormalities.
Over the years, in addition to myelodysplasia, he was given various diagnoses including Behcet's disease, antiphospholipid syndrome, and pyrexia of unknown origin responsive to steroids.

Drugs the patient was on at admission

These included warfarin for two previous confirmed episodes of deep venous thrombosis (left leg and right leg), glibenclamide for diabetes mellitus and prednisolone 10 mg per day.

Examination and investigations on his current presentation

Examination

He looked ill and pale. He had an urticarial right peri-orbital swelling as well as several tender 0.5–1.0 cm subcutaneous nodules felt over the extensor and flexor surfaces of both upper and lower limbs. There was no lymph node enlargement and no oral, respiratory, cardiovascular, abdominal, neurological, musculoskeletal or genital abnormalities.

Laboratory results

Hemoglobin 9.1, MCV 101.3, WBC 9.9, platelets 152, ESR 133, CRP 103, international normalized ratio (INR) 3.1.
Renal and liver function and urinalysis were normal.
Chest X-ray – normal.
Electrocardiogram – normal.

Management

The patient was given intravenous hydrocortisone 100 mg three times a day with a quick resolution of his symptoms and disappearance of his painful skin swellings. Within few weeks his ESR dropped to 33 mm/hr. On reducing his steroid dose to 10 mg per day of prednisolone, his facial urticaria recurred and he developed a left sided pleuritic chest pain. A chest radiograph confirmed a new left basal infiltrate and an associated small effusion. These again promptly resolved (within 48 hours) on increasing his steroid dose. Cyclosporin was then added as a possible steroid-sparing agent.

Bone marrow examination

A repeat bone marrow examination was performed.
Salient features of bone marrow aspirate: multilineage dysplasia involving the granulocytic, erythroid and megakaryocytic cell lines.
Erythroid dysplastic features including: increased mitosis, nuclear lobulation and extensive vacuolation.
Myeloid dysplastic features were found in at least 19% of the precursors. These features included pseudo Pelger-Huet anomaly, misshapen nuclei and increased vacuolation. Blasts made up about 2% of all nucleated cells. Normal amounts of stainable iron were present with normal numbers of sideroblasts. Pathologically ringed sideroblasts were not present.

Bone marrow core biopsy

Salient features of bone marrow core biopsy:
Pronounced hypercellularity (98–100%). The tri-lineage dysplasia was confirmed; the presence of micromegakaryocytes, the megalobastoid erythropoiesis and the presence of numerous mitotic figures. Especially noteworthy was the abnormal localization of immature myeloid precursors (ALIP). Lymphocytes and plasma cells were normal. Reticulin fibrosis was mildly increased and thinned-out bony trabeculae confirmed osteoporosis. Abnormal non-haemopoietic cells and/or granulomata were not present.

Discussion

The bone marrow findings were consistent with a myelodysplastic syndrome best classified as Refractory Cyctopenia with Multilineage Dysplasia (RCMD) The presence of ALIP is a negative prognostic feature although the low number of myeloblasts is prognostically favourable [2]. Cytogenetic studies were not available and this seriously hampered further characterization and prognostication [2] in this patient. A primary myelodysplastic syndrome is favoured over myelodysplasia secondary to azathioprine because dysplastic features preceded azathioprine exposure. We based our conclusion on the presence of abnormal oval macrocytic red cells, persistent and worsening anemia and recurrent thrombocytopenia (counts as low as 67,000/cmm were documented with no clear precipitant); abnormalities that were evident on his serial blood counts even before the azathioprine trial. The patient has been very healthy prior to his presentation and denied exposure to any chemicals or cytotoxic drugs. Presumably he suffers from a “benign” form of primary myelodysplasia considering that he has had it for more than four years so far and has still not developed any life threatening cytopenia. Cytogenetic analysis of the bone marrow would have been helpful to support a primary myelodysplastic syndrome by confirming the absence of multiple and/or complex cytogenetic abnormalities [2]. Although not all patients with MDS will exhibit genetic abnormalities, three types of gene mutations are noted in this illness [5]: (1) tyrosine kinase–RAS/BRAF signal transduction pathway genes activating mutations, leading to increased cell proliferation (Class I mutations); (2) hematopoietic transcription factors genes inactivating mutations resulting in disturbed cell differentiation (Class II mutations); and (3) inactivating mutations of the tumor suppressor gene p53. These mutations are associated

with complex balanced or unbalanced chromosomal material deletion, gain or translocation and are an essential component in disease pathogenesis, classification and therapy [5], [6]. Patients with de novo MDS in contrast to therapy-related MDS are more likely to have a normal karyotype (50–60% versus 5–10%) and less likely to have unbalanced chromosome 5 or 7 aberrations (15–25% versus 50–70%) [5].

The protean nature of this patient's signs and symptoms coupled with the complex clinical history made it difficult to find a unifying underlying diagnosis. Myelodysplastic syndrome (MDS) is that underlying pathology to explain the immunological steroid-responsive disease in this patient. The association between MDS and clinical immune dysfunction is well recognized [3], [4]. Our patient showed a relapsing-remitting disease pattern typical of autoimmune disease particularly on tapering down his immunosuppressive therapy. Multiple organ systems were involved including skin, lung parenchyma and serous cavities. In a series of 221 cases, 30 patients (14 percent) experienced autoimmune phenomenon of whom 7 patients had an acute systemic illness with fever, cutaneous vasculitis, arthritis and pulmonary infiltrate [7] – a syndrome similar to that of our patient. Other autoimmune associations of the myelodysplastic syndrome include pericarditis, pleural effusions, skin ulcerations, iritis, myositis, glomerulonephritis and peripheral neuropathy. Furthermore specific autoimmune diseases have also been reported including relapsing polychondritis, polymyalgia rheumatica, Raynaud phenomenon and Sjögren's syndrome, inflammatory bowel disease, pyoderma gangrenosum and Sweet's syndrome [7], [8], [9]. The pathophysiology of these autoimmune phenomena is not well understood. Organ specific as well as immune-complexes and generic auto-antibodies (apart from antinuclear antibodies in a minority of patients) are classically undetectable [8]. A broad disturbance of self-recognition mechanisms seems to be a general feature of patients with MDS [10]. A deficiency in the regulation of self-reactivity may thus contribute to the disease pathogenesis [10]. Fortunately, these so-called paraneoplastic autoimmune complications mostly respond to immunosuppressive agents (steroids, cyclosporin) with the occasionally non-responsive syndromes contributing to early patient mortality [7], [8], [9]. The management of the myelodysplastic syndrome is otherwise supportive with transfusions with packed red blood cells and platelets, as needed, and antibiotics for infective complications. However, newer approaches such as growth factor therapy (recombinant human granulocyte colony-stimulating factor (G-CSF), recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), and recombinant human erythropoietin-EPO), interleukin-11 therapy, thalidomide, tumour necrosis factor inhibitors (infliximab), cytotoxic agents (for blastic/acute myeloid leukaemia transformation) and bone marrow transplantation may be tried in selected patients [11], [12], [13], [14], [15]. In the myelodysplastic syndrome, DNA methylation curtails suppressor genes (p53 tumour suppressor gene) activity and increase the risk for acute myeloid leukaemia transformation. Use of powerful DNA hypomethylating pyrimidine analogue azacytidine and other recently FDA approved agent, decitabine, may reduce hypermethylation and induce re-expression of key tumor suppressor genes in myelodysplastic syndrome thus improving the long-term prognosis [15].

Notes

Competing interests

The authors declare that they have no competing interests.

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