Puzzling Fever and Neutropenia in a Patient with Crohn's Disease Post-Coronary Artery Bypass Surgery

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Key words: Crohn's disease, coronary artery bypass graft, neutropenia, fever of unknown origin

IMAJ 2002;4:1158–1161

Patient Description

A 43 year old man was admitted to the hospital for evaluation of 39°C fever with no other symptoms. A year earlier the patient was diagnosed with Crohn's disease, which involved the terminal ileum and manifested with fever, abdominal pain and diarrhea. Recently, the Crohn's disease was in remission, treated with rafassal (5-amino-salicylic acid) 3 g/day and methotrexate 12.5 mg weekly. In addition, the patient had ischemic heart disease with inferior wall myocardial infarction that was diagnosed 5 months before admission. Coronary angiography demonstrated triple-vessel disease, and an uneventful coronary artery bypass graft surgery was performed 5 weeks prior to his admission in another hospital. His recovery was as expected, and the treatment of decreasing dosages of prednisone ended a week before his admission.

His current illness began 5 days prior to admission; with a 39°C fever without chills and without any respiratory, urinary or gastrointestinal symptoms. He denied having an erythema. A persistent retrosternal pain had bothered him since his CABG surgery and had lately worsened. There was no relief from the pain while sitting and no change upon taking a deep breath. He denied any travel abroad, close contact with sick or infectious people, or eating unpasteurized goat cheese. Treatment with ciprofloxacin was initiated 3 days before admission. The patient had quit smoking 6 months previously. He did not drink alcohol regularly or use intravenous drugs. The family history was positive for a father with ischemic heart disease and a past history of CABG surgery.

On physical examination the patient appeared sick. He was shivering and his temperature was elevated at 38.5°C. His pulse was 97/minute and blood pressure 140/80 mmHg. A maculopapular eruption was noted on his upper chest, but no lymphadenopathy was detected. Heart sounds were normal, without murmurs or friction rub. The area over the sternum was tender to palpation; the lungs were normal to auscultation, but the abdomen was not tender. The liver was palpated at 2 cm below the costal margin, descending. The spleen was not enlarged. There was no evidence for deep vein thrombosis. Electrocardiogram showed sinus tachycardia rhythm, with pathological Q waves on L2,3 and aVF. Chest X-ray revealed a normal-sized heart without any infiltrates or pleural effusion. Initial laboratory tests showed: erythrocyte sedimentation rate 20/hour, total white blood cell count 1,730/mm^3 with 76% neutrophils, hemoglobin 13.7 g/dl, and platelet count 122,000/mm^3. He was diagnosed as having wound infection, and intravenous cloxacillin 4 g/day was initiated. However, the fever persisted with a remittent pattern and daily temperatures above 39°C. At the same time, a reduction in the total WBC count was noted, and especially the absolute neutrophil count, which reached a level of 600/mm^3 on the 5th day of his admission. Hemoglobin was stable at 13 g/dl and there was a slight stable thrombocytopenia with a platelet count of 130,000/mm^3. The hematologic findings are summarized in Table 1. Further tests, including creatine phosphokinase, bilirubin, protein and albumin, were normal. There was a mild liver function abnormality with alanine aminotransferase of 67 IU/L, aspartate aminotransferase 93 IU/L, and lactate dehydrogenase 406 IU/L. A summary of the blood chemical values is shown in Table 2. Additional tests – repeated aerobic and non-aerobic blood cultures and urine culture – were negative. Direct and indirect Coombs' test, antinuclear factor, and screening for hepatitis A, B and C as well as human immunodeficiency virus were negative. Serologic markers for acute Epstein-Barr virus and cytomegalovirus infection were negative. Purified protein derivative was negative. Echocardiography of the heart showed normal heart function with a minimal amount of pericardial fluid. Abdominal ultrasound was interpreted as normal, with no evidence for hepatosplenomegaly or retroperitoneal lymphadenopathy. Bone and gallium scans were negative. Bone marrow biopsy that was performed 10 days after admission was rich in all the cellular lineages; no maturation arrest was noted in the white cell lineage, and it was concluded to be a reactive, non-specific bone marrow.

A week after his admission, the lack of response to the intravenous antibiotics prompted us to initiate administration of prednisone 40 mg/day together with famotidine due to a possible post-pericardiotomy syndrome. Under this regimen his fever dropped to 36°C for the first time since his admisison, but again rose to 40°C. During the hospitalization the patient lost 4 kg and complained of diffuse body aches and pains. In the third week of his admission a diagnostic procedure was conducted.

CABG = coronary artery bypass graft

WBC = white blood cell

Table 1. Hematologic laboratory variables

	Before admission	Day 1	Day 5	Day 10
Hemoglobin (g/dl)	13.5	13.7	12.6	12.6
Mean corpuscular volume (μm^3)		95	93	94
WBC (per mm^3)	7.4	1.7	1.5	1.3
Neutrophils (%)	52	69	41	47
Total neutrophils		1.1	0.6	0.6
Platelet count (per mm^3)	319	122	144	53

Table 2. Blood chemical values

	Day 5 of admission	Day 10 of admission
Bilirubin, total	0.5	0.7
Protein (g/dl)	5.7	5.9
Albumin (g/dl)	3.4	3.4
Alanine aminotransferase (U/L)	67	28
Aspartate aminotransferase (U/L)	93	53
Lactate dehydrogenase (U/L)	406	405
Alkaline phosphatase (U/L)	223	210
Cholesterol	116	127

Differential diagnosis

Pnina Rotman: This 43 year old man with non-active Crohn's disease was treated regularly with rafassal and methotrexate. He was also known to have ischemic heart disease and underwent an uneventful CABG surgery 5 weeks before his admission. He was admitted to the internal medicine department because of a febrile disease that started 5 days prior to his admission, accompanied by moderate neutropenia and mild thrombocytopenia, with no apparent change in hemoglobin values. The fever did not respond to various antibiotic regimens as well as prednisone in a maximal dose. His physical examination was unrevealing, apart from a marked tenderness above the sternum around his scar. His workup did not show evidence of pericardial or pleural fluid. Abdominal ultrasonography was interpreted as normal, as were bone and gallium scans.

The prominent features of this case are prolonged fever and neutropenia. According to the current definitions by Durack and Street [1] from the 1991 classic, fever of unknown origin is defined as fever above 38.3°C for 3 weeks, during 3 days of hospitalization, or during two outpatient visits. The prolonged fever of our patient fit this definition. The absolute neutrophil count is calculated by multiplying the total WBC count by the percentage of neutrophils plus bands. Accordingly, mild neutropenia is defined as ANC of 1,000–1,500 cells/mm^3, moderate neutropenia corresponds to an ANC of 500–1,000/mm^3, and in severe neutropenia the ANC is below 500 cells/mm^3 [2]. Despite his marked neutropenia, the patient did not have "neutropenic fever." In fact, our patient had *fever with neutropenia*. He was not treated with any chemotherapeutic agent to induce a neutropenic state, and his neutropenia accompanied his fever and was part of the febrile illness. A WBC count that was performed 3 weeks before his admission showed a total WBC count as high as 7,400/mm^3, however on the day of his admission the total WBC count was already low at 1,100/mm^3. The granulopenia worsened during his hospitalization, with a nadir granulocyte count of 600/mm^3 that was observed from the 5th day of his hospitalization on.

The reasons for FUO are multiple, but most cases belong to one of the following groups: infections, neoplasms, connective tissue diseases, miscellaneous disorders, and undiagnosed diseases. Infections are the leading cause of FUO and account for 20–25% of all cases in most series. As Mackowiak and Durack stated [1], most often the cause of FUO is a common disease presenting in an atypical way, rather than an uncommon disease with a typical presentation. This assumption will guide us in the differential diagnosis of our case.

Can we learn from the fever pattern about its etiology? The answer is no. Fever patterns are neither sensitive nor specific enough to be considered diagnostic for any disease. An exception would be malaria with its typical tertian or quatrain fever. Moreover, there is no correlation between the height of the fever and the presence of bacteremia. Additionally, verifying the presence of fever is essential: in a series of 347 patients admitted to the National Institutes of Health due to prolonged fever, 35% were ultimately determined as not having fever [3].

Is there a link between Crohn's disease, neutropenia and FUO? The extra-intestinal manifestations of Crohn's disease are prevalent and include rheumatologic, dermatologic, ocular, hepatobiliary, and urologic manifestations. The typical hematologic manifestations include iron deficiency anemia due to gastrointestinal bleeding, and a macrocytic anemia due to B12 deficiency or sulfasalazine treatment. There are anecdotal reports on 12 patients with Crohn's disease who developed pancytopenia after or coincidental to a diagnosis of Crohn's disease [4]. In addition, there is a report of cyclic neutropenia in a patient with Crohn's disease [5]. Thus, the link between Crohn's disease and neutropenia is only anecdotal.

Because our patient had Crohn's disease he was treated with two drugs: rafassal and methotrexate. Both have typical hematologic side effects and both can cause drug fever. Rafassal or 5-aminosalicylic acid or mesalamine does not contain a sulpha derivative, and therefore has fewer side effects. The active component is released in the terminal ileum and colon and acts by inhibition of production of local prostaglandins and leukotrienes. The literature includes 12 case reports of neutropenia caused by mesalamine [6,7]. Alternatively, methotrexate is given in inflammatory bowel diseases to maintain remission and as a steroid-sparing agent. Our patient was treated with a low dose methotrexate, 12.5 mg/week, yet even this dose can cause hematologic side effects. Until 1997 a total of 83 cases of blood dyscrasias were reported in England that were associated with low dose methotrexate, of which 36 were fatal [8]. While the most common hematologic side effect known to be associated with methotrexate is megaloblastic anemia, various pancytopenias were reported. Accordingly, if methotrexate caused our patient's neutropenia, we would expect to see typical macrocytic characteristics in his red blood cells.

ANC = absolute neutrophil count

FUO = fever of unknown origin

Any drug can cause drug fever. A comprehensive study on this topic [9] had some interesting conclusions. In contrast to earlier beliefs, in most of the cases there was no relative bradycardia; concurrent eosinophilia or erythema is not common; and there is no typical fever pattern. In addition, the lag time between initiation of the drug and appearance of the fever is variable, with an average of 21 days. The list of drugs that may be involved in drug fever is considerable, however the exact prevalence of drug fever is not known. Finally, stopping the medication will result in disappearance of the fever within 1–3 days [9]. Nonetheless, in our case the clinical picture included more than just fever and, therefore, could not be explained by drug fever alone.

Our patient underwent CABG surgery 5 weeks before admission and had local tenderness at the surgical wound. Although a superficial wound infection after CABG is common, a deep wound infection is infrequent and occurs in 3% of patients. Osteomyelitis of the sternum or mediastinitis can cause high fever but not leukopenia. The physical findings are usually more impressive and may include sternum instability. It is noteworthy that our patient did not have risk factors for developing mediastinitis such as diabetes, obesity, previous sternotomy, chronic obstructive lung disease, smoking, etc [10].

Another surgical complication, post-pericardiotomy syndrome, appears usually 1–4 weeks after a surgical procedure that involves opening the pericard, and can appear even later. Seen in 18% of patients, post-pericardiotomy syndrome usually causes pericarditis, pleuritis or pneumonitis, and can also cause high fever. The syndrome is characterized by ESR, leukocytosis and ECG changes [11]. Our patient did not have elevated ESR and, in addition, did not have pericarditis, pleuritis or pneumonitis. After exclusion of several diagnoses that might be related to the patient's medical history, we will focus on diseases that cause fever and neutropenia. As mentioned earlier, the bone marrow biopsy that was obtained a week after the patients' admission was surprisingly normal. All three myeloid cell series were present, in all maturational stages.

The neutropenias are categorized as congenital or acquired. The common causes for acquired neutropenia include infections, which are the most common, drugs, and immune neutropenia [2]. It does not seem likely that any one of the patient's medications was the cause of his neutropenia. Immune neutropenia is caused by an autoimmune destruction of neutrophils by antineutrophil antibodies. This autoimmune destruction is similar to platelet destruction in idiopathic thrombocytopenic purpura and to red blood cell destruction in autoimmune hemolytic anemia. The antibodies can be directed against mature neutrophils as well as myeloid precursors. Usually, antibodies that are produced against a foreign antigen cross-react with antigens on the envelope of the neutrophil. The bone marrow is hypercellular or normocellular, but lacks mature neutrophils. Autoimmune neutropenia can be the sole manifestation of a disease, can be induced by infections or medications, or may be part of an autoimmune disease. It can also appear after recurrent blood transfusions [2].

The most common cause of acquired neutropenia is infection. A long list of infections can cause neutropenia, including bacterial, fungal, rickettsial, protozoal, and viral. Infections cause neutropenia by different destructive mechanisms: antibodies, activation of the complement cascade, and toxic inhibition of myeloid precursors. More than one infection could have been the cause of our patient's illness.

Miliary tuberculosis should be considered in our case. Miliary TB usually presents as fever of unknown origin with a normal chest X-ray and negative tuberculin test. Characteristically, patients have pancytopenia and sometimes myelofibrosis. Our patient did not have elevated ESR, he did not present with normocytic normochromic anemia, and, moreover, he did not have night sweats and did not lose weight. Among the many viral infections that can cause neutropenia, the likely ones in our case would be those that can be transferred via blood units. Cytomegalovirus is acquired spontaneously or via blood transfusion. The disease begins 20–60 days after exposure and can last up to 6 weeks. Patients suffer from high fever, headache, weakness and myalgia. They may have splenomegaly, leukocytosis or leukopenia. The ESR is not significantly enhanced. Other viruses that share a similar picture are EBV, hepatitis B and C, and HIV. Acute HIV syndrome is the clinical syndrome that appears during the primary HIV viremia, and usually manifests with fever, pharyngitis, lymphadenopathy and headache. Even after the screening procedures that are currently performed in blood banks, HIV virus is still transferred in 1:450,000 to 1:600,000 blood units.

Another virus that can be transferred by blood units is parvovirus. Contained in 1:20,000–1:50,000 blood units [12], it is the smallest DNA virus, around 5,000 DNA bases long. This virus has great affinity to red blood cells, and after infecting them it activates an apoptotic mechanism that leads to their destruction. The virus was first attributed to human diseases in 1975. It is quite prevalent; according to serologic tests around 50% of the population have been exposed to it by the age of 15 [13]. There are various clinical pictures, each depending on the immunologic and hematologic condition of the host. Fifth disease, for example, is an acute childhood disease that typically manifests with a slapped cheek appearance. Transient aplastic crisis was first described in patients with sickle cell anemia, thalassemia and other hemolytic states. Additionally, the virus can cause hydrops fetalis in pregnant women and persistent anemia in immunocompromised hosts [13]. In healthy people the disease has two phases: the first one is characterized by fever chills and myalgia and appears in the second week of the illness. The second phase is characterized by erythema and arthralgia, and towards the end of this phase the hemoglobin drops [13]. Even though the disease is self-limited it can be quite severe. Patients may have prolonged fever, weakness and dyspnea. While the typical hematologic effect of parvovirus is erythroid hypoplasia, patients with neutropenia and thrombocytopenia due to parvovirus have also been described [14–16]. The diagnosis is serologic with specific immunoglobulin M that rises a few days after the initial viremia and remains elevated for 2 months. Polymerase

ESR = erythrocyte sedimentation rate
ECG = electrocardiogram

EBV = Epstein-Barr virus
HIV = human immunodeficiency virus

chain reaction for viral DNA from the bone marrow can be diagnostic throughout the disease.

In summary, I believe that our patient's illness was caused by a parvovirus infection. The infection caused the prolonged fever and the neutropenia. The patient might have been exposed to the virus during his CABG surgery when he probably received blood units. He was partially immunocompromised due to the low dose methotrexate and steroid treatment that he had received before his admission. It could very well be that the prolonged clinical picture was partially due to his immune status. The clinical symptoms of our patient were not specific but were described in parvovirus infection: i.e., prolonged fever without lymphadenopathy and without significant hepatosplenomegaly, accompanied by arthralgia and mild maculopapular eruption. Our case is unique in the discrepancy between lack of effect on the red blood cells and a dramatic effect on the white blood cells. Similar cases have been reported [14–16]. I think that the diagnostic procedure was the serologic testing, but it might have included a PCR test from the bone marrow specimen for the viral DNA. Both tests are diagnostic for parvovirus infection.

Yair Levy: The diagnosis of this patient was parvovirus. It is based on a blood test that showed positive IgM and IgG antibodies. The diagnosis was confirmed by PCR analysis of bone marrow.

Parvoviridae are among the smallest known DNA-containing viruses that infect mammalian cells. Parvovirus B19, like the other autonomous parvoviruses, is dependent on mitotically active cells for replication. However, B19 has a very narrow target cell range and apparently can be propagated only in human (or primate) erythroid cells. The virus cannot easily be cultivated in the laboratory. Parvovirus B19 infection is common in childhood, yet infection also occurs in adult life [16]. Most parvovirus infections, especially in children, remain asymptomatic or are diagnosed as non-specific viral illness. The viral DNA has been found in the respiratory secretions of patients at the time of viremia, suggesting that the infection is generally spread via a respiratory route of transmission [17]. The antibody response is associated with the second phase of clinical illness characterized by rash and joint symptoms. Onset of the antiparvovirus B19 IgG antibody response occurs almost concurrently with the IgM response. The anti-B19 IgM antibody response is usually positive for 2 months after the acute illness and may wane shortly thereafter. The diagnosis of parvovirus can be made during the initial viremia by detecting virions in serum with immune electron microscopy. Parvovirus B19 DNA may be detected also during the initial viremia, however because adult patients usually present after onset of joint symptoms the most useful diagnostic test is anti-parvovirus B19 IgM serology.

Infection by the human parvovirus B19 can lead to various clinical manifestations as arthritis, cytopenia and hepatitis [17]. The most remarkable clinical features in our patient were fever and severe neutropenia. Although fever is a common feature of parvovirus B19 infection, FUO is rare and only a few cases have been described in the medical literature [18].

PCR = polymerase chain reaction
Ig = immunoglobulin

The patient was discharged from the hospital without fever after the final diagnosis was made. One month later he was hospitalized again with fever and neck pain. A diagnosis of subacute thyroiditis was reached and confirmed by thyroid iodide uptake scan. His IgM antibody to parvovirus was still positive. Subacute thyroiditis associated with parvovirus infection was documented only once in the literature [19]. Our patient was then lost to follow-up and 3 years later was killed in a road accident.

Parvovirus infection may be the new great imitator of our time due to its versatile clinical manifestations. Physician awareness regarding this interesting infection can easily lead to an accurate diagnosis.

References

1. Mackowiak PA, Durack DV. Fever of unknown origin. In: Mandell GL, Bennett JE, Dolin R, eds. Principals and Practice of Infectious Diseases. Chap. 44. Philadelphia: Churchill Livingstone, 2000:622–33.
2. Watts RG. Neutropenia. In: Lee GR, Bitchell TC, Foerster J, Athens JW, Lukens JN, eds. Wintrobe's Clinical Hematology. Chap. 73, 10th edn. Philadelphia: Lea & Febiger, 2000.
3. Aduan RP, Fauci AS, Dale DC, Wolff SM. Prolonged fever of unknown origin (FUO): a prospective study of 347 patients. *Clin Res* 1978;26:558A.
4. Bosch X, Bernadish O, Vera M. The association between Crohn's disease and the myelodysplastic syndromes. Report of 3 cases and review of the literature. *Medicine (Baltimore)* 1998;77:371–7.
5. Fata F, Myers P, Addeo J, Grinberg M, Nawabi I, Cappell MS. Cyclic neutropenia in a patient with Crohn's ileocolitis: efficacy of granulocyte colony stimulating factor. *J Clin Gastroenterol* 1997;24:253–6.
6. Committee on Safety of Medicine/Medicines Control Agency. Blood dyscrasias and mesalamine. *Curr Prob* 1995;21:5–6.
7. Wyatt S, Joyner MV, Daneshmend TK. Filgastrim for mesalamine-associated neutropenia. *Lancet* 1993;341:1476.
8. Committee on Safety of Medicine/Medicines Control Agency. Blood dyscrasias and other ADRs with low-dose methotrexate. *Curr Prob* 1997;23:12.
9. Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. *Ann Intern Med* 1987;106:728–33.
10. Zacharias A, Habib RH. Factors predisposing to median sternotomy complications. Deep vs superficial infection. *Chest* 1996;110:1173–8.
11. Kahn AH. The postcardiac injury syndromes. *Clin Cardiol* 1992;15:67–72.
12. Brown KE, Young NS, Barbosa LH. Parvovirus B19: implications for transfusion medicine. Summary of a workshop. *Transfusion* 2001;41:130–5.
13. Brown KE. Parvovirus B19. In: Mandell GL, Bennett JE, Dolin R, eds. Principals and Practice of Infectious Diseases. Chap. 136. Philadelphia: Churchill Livingstone, 2000:1685–93.
14. Saunders PWG, Reid MM, Cohen BJ. Human parvovirus induced cytopenias: a report of five cases [Letter]. *Br J Hematol* 1986;63:407–10.
15. Barlow GD, McKendrick MW. Parvovirus B19 causing leucopenia and neutropenia in a healthy adult. *J Infect* 2000;40:192–4.
16. Cohen BJ, Buckley MM. The prevalence of antibody to human parvovirus B19 in England and Wales. *J Med Microbiol* 1988;25:151–3.
17. Cohen B. Parvovirus B19: an expanding spectrum of disease. *Br Med J* 1995;311:1549–52.
18. Tabak F, Mert A, Ozturk R, Koksal V, Akbas I, Aktuglu Y. Prolonged fever caused by parvovirus B19-induced meningitis: case report and review. *Clin Infect Dis* 1999;29:446–7.
19. Vejlgaard TB, Nielsen OB. Subacute thyroiditis in parvovirus B19 infection. *Ugeskr Laeger* 1994;156:6039–40.

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