EASILY MISSED?

Febrile neutropenia

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. If you would like to suggest a topic for this series please email us (easilymissed.bmj@bmjgroup.com).

The definition of febrile neutropenia varies but is generally regarded as the presence of a fever >38°C with an absolute neutrophil count of <1.0×10^9/L. Febrile neutropenia is a result of bone marrow suppression, a common side effect of chemotherapy. Patients with neutropenia are susceptible to developing life threatening bacterial infection. Infection should also be considered in any systemically unwell patient receiving chemotherapy, even if no fever is present.

Why is it missed?

Cases of febrile neutropenia continue to be missed at initial presentation, as medicolegal reports and the 2008 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) show.[5-7] National guidance states that all patients receiving chemotherapy should be given both verbal and written information about their treatment, likely side effects, and details of whom to contact if problems arise.[4] Many patients will have access to a dedicated chemotherapy helpline, but this is not universal and not always used.[5] The 2008 national enquiry also found that among patients who became unwell while receiving chemotherapy, only 19% phoned a chemotherapy helpline, 32% contacted their general practitioner, and 41% attended an emergency department as first point of contact.[5]

Cases of febrile neutropenia may be missed because it is not considered.[6 7] Patients may not necessarily volunteer that they are receiving chemotherapy because they may assume that their own doctor knows about their treatment, and doctors handling calls out of hours in primary care centres may not have access to the patient record and may not ask. Finally, the seriousness of febrile neutropenia may not be recognised. An inability to mount an adequate inflammatory response means the signs and symptoms of infection may be minimal, particularly in those receiving corticosteroids. Patients may initially appear well, providing false reassurance to doctors, patients, and carers (case scenario).

KEY POINTS

Suspect febrile neutropenia in patients receiving chemotherapy who develop a fever of 38°C or higher or appear systemically unwell

Remember to ask patients with a recent diagnosis of cancer if they are receiving chemotherapy as they may not always offer this information

In all cases of suspected febrile neutropenia, refer the patient to hospital (ideally to their treating team) for an urgent full blood count, assessment, and consideration of immediate antibiotic treatment. Do not wait for results of a full blood count test sent from the surgery, as patients may decompensate rapidly

CASE SCENARIO

A 33 year old man presented to his local district hospital a week after chemotherapy, stating that he had a moist cough, with a fever of 38.8°C at home. As he had no fever and appeared well on examination, with no abnormal chest findings, he was prescribed amoxicillin and discharged. Over the next 24 hours he became increasingly unwell and presented at the emergency department with septic shock and severe neutropenia (neutrophils 0.02×10^9/L). Despite fluids and broad spectrum antibiotics, the patient died.

Why does this matter?

Even when treated appropriately, febrile neutropenia carries an overall mortality of about 5%.[1 8] Patients can quickly decompensate, and even short delays in treatment can be clinically important. Therefore all patients with a fever who are receiving chemotherapy should be referred immediately for assessment (ideally by their treating oncology team) and an urgent full blood count.

National guidelines state that all patients should receive (intravenous broad spectrum) antibiotics within 60 minutes.[4]

How is it diagnosed?

Clinical

The diagnosis of febrile neutropenia in primary care is a clinical one and requires general practitioners to be vigilant. Specifically ask patients with a recent diagnosis of cancer if they have recently had chemotherapy. Remember that haematological malignancies can cause myelosuppression in patients who have not received treatment. Timing may give guidance on a patient's risk of being neutropenic—for example, in patients with solid malignancies receiving chemotherapy every three weeks, the risk of neutropenia is typically greatest from day 7 to day 14. However, timing is often unpredictable and should not therefore be relied on.

Patients' symptoms are often non-specific with no localising features. Symptoms may include feeling hot or cold, rigors, sweats, influenza-like symptoms, and general malaise. Ask about sore mouth and diarrhoea, which also commonly occur after chemotherapy, as mucositis can be a portal of entry for host flora into the bloodstream.

Clinical examination should aim to establish quickly how unwell the patient is. Check the temperature and specifically look for signs of shock. This is more likely in patients with dyspnoea, dehydration, diarrhoea, and altered mental state.[9] Look for a focus of infection, although this is often not apparent. In patients with indwelling central venous lines, check the subcutaneous

HOW COMMON IS FEBRILE NEUTROPENIA?

The risk of febrile neutropenia varies widely (5%-50%) depending on the chemotherapy regimen[1-3]

The number of patients receiving chemotherapy each year in England is increasing[4]

An estimated 65 000 chemotherapy programmes (a planned period of repeated cycles of treatment) are delivered annually in England.[4] On the basis of this figure, we conservatively estimate that at least 10 000 episodes of febrile neutropenia occur annually

Risk increases with age (65 years and over), advanced stage of disease, presence of comorbidities, haematological malignancy, and absence of haematopoietic colony-stimulating factors support, and if a patient has had a previous episode of febrile neutropenia[3]

portion of the line and its exit site for signs of infection. Ask specifically about rigors associated with flushing the line as this may also indicate an infection associated with the line.

Investigations

If febrile neutropenia is suspected, refer the patient immediately to hospital (ideally to his or her treating team) for an urgent full blood count, where appropriate cultures, other blood tests, and radiological investigations can also be performed.

How is it managed?

Primary care doctors should ideally discuss patients with the treating department if they have any concerns about the management of unwell patients receiving chemotherapy. After admission to hospital, empiric broad spectrum intravenous antibiotics, according to the local policy on febrile neutropenia, should be promptly administered. This should be done before the full blood count result is known if the patient is in shock. Additional supportive measures, such as administration of intravenous fluids, may be necessary initially. The use of colony stimulating factors can be considered in patients at high risk, such as with expected prolonged (>10 days) or profound ($<0.1\times10^9$/L) neutropenia, hypotension, and multiorgan failure.[1] Stratification tools are sometimes used in secondary care to identify patients at low risk who can be treated safely with oral antibiotics in hospital with subsequent early discharge.[10]

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- Carcinoid syndrome (*BMJ* 2010;341:c3941)

A PATIENT'S JOURNEY

Rheumatoid arthritis

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Ailsa Bosworth was about 30 years old when she was diagnosed with seronegative rheumatoid arthritis. She describes her journey with the disease that led her to found a national charity, the National Rheumatoid Arthritis Society

My father had ankylosing spondylitis with active peripheral arthritis and iritis and was severely ill all his life. He died early from a stroke at age 62. Despite this family history, when I started to experience symptoms of a painful, swollen knee, it didn't occur to me that I might have inflammatory arthritis. My parents' generation kept their health problems private and didn't really share their difficulties with their children. So although I was aware my father had something called spondylitis and was taking various drugs, I didn't really understand what this meant, what caused it, or what the future might hold for him, or me.

The diagnosis

Rheumatoid arthritis is painful and disabling. It is not well understood by the general public, who hear the word arthritis and interpret it as osteoarthritis, a quite different disease. This is a source of great irritation to

This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

A CLINICIAN'S PERSPECTIVE

I first met Ailsa when I took over her care in 2002. She had a 20 year history of a severe seronegative inflammatory polyarthritis. This had resulted in widespread joint damage and disability. As with many patients with inflammatory arthritis, Ailsa had been treated with many traditional disease modifying drugs, which had largely failed to suppress her arthritis.

Of all the treatments that Ailsa had previously received, the combination of low dose oral methotrexate plus intravenous infliximab (a TNF-α inhibitor) in the context of a clinical trial had been her most effective treatment. Over the next couple of years she was converted to a higher dose of methotrexate plus adalimumab (a self administered subcutaneous TNF-α inhibitor). This improved control of her arthritis, and she was gradually weaned off her long term oral prednisolone. Despite this improvement the legacy of persistent joint inflammation over more than two decades has necessitated further prosthetic joint surgery over recent years. Ailsa's management has required close clinical interaction between rheumatologist, specialist nurses, specialist orthopaedic surgeons, and her general practitioner. Access to such a multidisciplinary approach for patients with complex inflammatory arthritis is essential, yet the financial constraints in the NHS make this increasingly difficult to maintain.

The prognosis of patients with rheumatoid arthritis and other inflammatory arthropathies has improved considerably over recent years. Earlier diagnosis, more aggressive treatment with disease modifying drugs (often in combination), and increasing access to biological agents have all contributed to this improvement. Nevertheless, clinical "remission" is not the rule, with many patients still developing progressive deformity and disability.

During my initial consultation with Ailsa in 2002 she mentioned to me how she had recently started the National Rheumatoid Arthritis Society from her own home with the help of a few volunteers. The society is now a prominent and important patient organisation with a national profile. It provides both support and a "mouth piece" for patients with rheumatoid arthritis in this country. These days our outpatient consultations and her surgical procedures are fitted in between her commitments to local, national, or international rheumatology meetings or working parties. The consultations generally start with a discussion of what I can do to help Ailsa with the management of her arthritis, invariably followed by an offer from Ailsa about what the National Rheumatoid Arthritis Society can do to help us and our patients.

There are of course many challenges in working with patients with inflammatory arthritis, particularly an "expert patient" who knows the outcome of the clinical trial or the NICE guidance before you do. However, Ailsa is an example of how an individual with the right personal attributes can use adversity as a motivation for supporting both fellow patients and the healthcare professionals who are privileged to care for them.

Alan Steuer, consultant rheumatologist

people with rheumatoid arthritis. A major cause of delay in diagnosis is people's failure to recognise that their symptoms indicate potentially serious and incurable illness. This is probably why it took 9 months before my boss forced me to go and see a general practitioner, by which time I could barely walk. The general practitioner referred me immediately to a rheumatologist, and rheumatoid arthritis was diagnosed straight away. I found myself in hospital having my knee aspirated and injected with steroid, and my whole leg was put into plaster. As soon as the cast came off and I started walking around again, the knee filled up. I can't now remember how many times it was aspirated.

I had my daughter in 1982, having taken five years to get pregnant—I didn't know then that rheumatoid arthritis can affect fertility. I was well during my pregnancy, as is often the case, but the disease flared up badly after Anna was born and went everywhere in my body, attacking particularly my knees, hands, wrists, and elbows. I remember having difficulty in holding and lifting my daughter. By the time she was 9 months old, I was in hospital having my first operation—a right knee synovectomy, which was extremely painful with a long recovery period. I was fortunate to have a nanny to help me as I had gone back to work when Anna was 3 months old, and despite severe disease and 17 operations, I have always worked and wanted to work.

In 1984 I was made a director of the company I was working for and I was determined that rheumatoid arthritis was not going to prevent me achieving my goals.

Treatment then and now

The treatment I received in those early years was very different from the treatment received by people with a new diagnosis these days. All I was given for the first three years, despite severe disease and visible bone erosions in x ray films, were pain killers and non-steroidal anti-inflammatories. The disease modifying drugs, which were considered to be very toxic and were given only when a patient had become extremely ill and disabled are now given immediately on diagnosis. I was hospitalised several times when things got really bad; I had lost weight and was about 48 kg and was beginning to despair. The treatment that I was receiving (or lack of it) was usually causing me to be in tears after my clinic visits. Fortunately a medical friend who could see the trouble I was in did some research and recommended an eminent rheumatologist. I immediately sought referral to him from my general practitioner.

At last, someone who could help

By the time I was sitting in front of my new consultant, I was a week away from a second synovectomy, this time on my left knee, which I was dreading. He took a thorough history, arranged blood tests and radiography and announced that I didn't need the operation. I was delighted. He prescribed me steroids, which I felt at the time literally saved my life. However, I didn't realise then that I would be on a low dose of steroids for some 20 years. With hindsight, I would have tried to wean myself off them at a much earlier stage had I known the damage they would do. In fact, if someone had sat me down and told me what I would be facing over the coming years, I would have been horrified and terrified; perhaps it is just as well that we can't see into the future but must deal with things as they occur.

Disease modifying drugs did not help me

Over the next decade I tried penicillamine, sulfasalazine, hydroxychloroquine, oral and parenteral methotrexate and had gold injections for five years. Nothing

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- At sixes and sevens: prostate cancer (*BMJ* 2010;341:c3834)

NATIONAL RHEUMATOID ARTHRITIS SOCIETY

This battle, and the feeling that there was no one to help me, led to my starting the National Rheumatoid Arthritis Society (NRAS, www.nras.org.uk) in 2001, with great support from some wonderful rheumatologists. The society operated from my home at first, moving in 2004 to its current offices, where we now have 20 staff. The NRAS is providing valuable services for people with rheumatoid arthritis—I like to think of it as a one-stop shop for people living with the disease—and everyone at the NRAS is dedicated to improving the quality of life for people living with this awful disease.

worked. I continued to erode, and I had four operations on my hands and wrists to repair ruptured tendons, excise the ulnar styloid on both wrists, and fuse both wrists with Stanley pins. Each operation meant that an arm was out of action for three months, which wreaked havoc with my life: I couldn't drive, cook, wash or dry my hair myself, get dressed, type normally, and so on. I also had hip replacement surgery, during which I lost so much blood that my haemoglobin levels dropped so low that I had to have a blood transfusion. During a previous spell in hospital for bed rest the doctors had established that I had pernicious anaemia, and so after many iron injections, I was switched to monthly B-12 injections, which I must now have every three months for the rest of my life.

Desperation and hope

In 2000 my consultant managed to get me on to a trial of infliximab, a new anti-TNF (anti-tumour necrosis factor) drug, at Guy's Hospital in London. I was desperate. Nothing had worked for me, and only the steroids were enabling me to function at all. Within an hour and a half of receiving the first infusion, I could feel a positive difference. I wasn't so stiff and painful. I could see a glimmer of hope that maybe things could be different, and after four months of taking the drug I was getting my life back. At the end of the trial I was devastated to be taken off the drug and told I wouldn't be able to get it because no one would fund it. I found this incredible, and it took six months of fighting to get myself back on treatment.

The impact on my life

It took me a long time to come to terms with the impact of rheumatoid arthritis on my life. I used to be very active: I danced, rode horses, did snow and water skiing, played tennis, and loved walking, but bit by bit I was having to give up all these things. When I couldn't wear heels any longer I had to change my whole wardrobe to accommodate shoes I didn't like. I put off applying for a blue badge because I couldn't face being referred to as disabled. My arthritis has affected not just me, but my family. Every time I went into hospital for more surgery, my young daughter used to think that I was going to die, and we always had to spend time consoling and reassuring her that I really was going to come home again.

Since 2000 I have had posterior and anterior cervical spine fusion of C4 and C5, both elbows replaced, a left total knee replacement, right hip replacement, triple arthrodesis to my left foot, both ankles replaced, and reconstruction of my left foot and ankle. I have also had iritis, which has left me unable to see out of my right eye. I am due to have a vitrectomy on this eye in the hope that once the debris caused by the inflammation has been removed, a contact lens may enable me to see more clearly. I do hope so as the lack of vision in that eye interferes with the good sight in my other eye, which I pray will remain. The thought of this happening in my good eye is something that I cannot contemplate; it would be devastating.

I would like to acknowledge that my life would be very different without the unstinting support of my husband, my family, the amazing team at the National Rheumatoid Arthritis Society, and my responsive rheumatology team.

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Attaining energy balance with the must-have toys this Christmas

Scooters and the Lets Cook and Girl Gourmet range of toys are reported to be among the must-have presents for Christmas this year.[1] With Lets Cook and Girl Gourmet toys, children can make cupcakes, smoothies, ice cream, and candy jewellery. While these food themed toys may at least teach basic cookery skills, they are likely to add to the calorie count of a child's diet. Changes in diet and physical activity are regularly reported to be the main drivers of the present obesity epidemic,[2] and yet are also suggested as being the most easily modifiable risk factors in children.[3]

Therefore, we investigated the energy expended while using a Micro Scooter in relation to the calorie content of a Gourmet Girl cupcake. A 20 kg child would need to scoot for an hour on a Micro Scooter to burn off the 125 kcal contained in every cake.

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