CME Article

How we evaluate and treat neutropenia in adults

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Isolated neutropenia is a common clinical problem seen by primary care physicians and hematologists. The evaluation of neutropenia is dictated by the acuity of the clinical presentation and the duration, age, and clinical status of the patient. In this review, we provide a practical approach to the evaluation of the adult patient with neutropenia, with the major focus on the evaluation of neutropenia in the outpatient setting. (*Blood*. 2014; 124(8):1251-1258)

Introduction

Isolated neutropenia without concomitant anemia or thrombocytopenia is a common clinical problem seen by primary care physicians and hematologists. The etiologies of neutropenia vary from transient suppression by self-limited viral illnesses to previously undetected congenital syndromes to serious systemic diseases. The clinical significance likewise ranges from a mild laboratory abnormality with no detectable consequence to a severe disorder characterized by recurrent, life-threatening infections. Consequently, determining how extensive an evaluation is necessary and whether intervention is required can be challenging. This review discusses the evaluation and management of the neutropenic adult patient, as well as the pathophysiology of specific neutropenia syndromes.

We begin by presenting the following 3 case vignettes, to which we will refer periodically during the review, to help illustrate aspects of the evaluation and management of neutropenic adults.

Patient 1

A 29-year-old man from Ethiopia presented for evaluation of neutropenia. He had no significant past medical history. Of note, he had not experienced any infections other than a brief, self-limited episode of sinusitis earlier that year since his arrival in the United States five years prior. His examination was unremarkable. His primary care physician obtained a complete blood count (CBC) panel as part of a new patient visit. The differential demonstrated a mild neutropenia (28% polymorphonuclear neutrophils, calculating to an absolute neutrophil count of 1100). Otherwise the peripheral smear was unremarkable. He did not remember having had a previous CBC panel.

Patient 2

An 80-year-old man presented for an evaluation of neutropenia. This was detected incidentally by his primary care physician 2 years earlier and had initially been mild, but had steadily worsened in the time since. He recently had an episode of severe pharyngitis and on evaluation was found to have an absolute neutrophil count (ANC) of 100. Subsequently, he developed several skin lesions that demonstrated slow healing and required antibiotics. A bone marrow

Table 1. Causes of neutropenia in adults

Congenital*
Constitutional neutropenia
Ethnic neutropenia
Benign familial neutropenia
Cyclic neutropenia
Acquired
Infection-associated
Post-infectious
Active infection (sepsis, viruses)
Drug-induced
Agranulocytosis
Mild neutropenia
Autoimmune
Primary autoimmune
Secondary autoimmune
Felty syndrome
Malignancy
Acute leukemia
Myelodysplasia
LGL leukemia
Myeloma, lymphoma
Myelophthisic processes
Dietary
B$_{12}$, folate deficiency
Copper deficiency
Global caloric malnutrition

*Excludes forms of congenital neutropenia that would be diagnosed in childhood (eg, severe congenital neutropenia or neutropenia occurring in the context of a larger congenital syndrome).

biopsy showed myeloid hypoplasia but was otherwise unremarkable. He was started on methotrexate 12.5 mg weekly; 4 weeks later, his ANC had risen to 950.

Patient 3

A 53-year-old woman presented for an evaluation of neutropenia. She had previously been well, although she had dealt with intermittent sinus infections for many years. Eighteen months prior, she was hospitalized for diverticulitis. During that admission, she was noted to be neutropenic, and her ANC had not recovered since that time. Her ANC was 320, hemoglobin 11.3 μg/dL, and platelets 320 000. Peripheral flow cytometry showed no evidence of lymphoma or large granular lymphocyte (LGL) leukemia. Bone marrow biopsy showed a normocellular marrow with maturing trilineage hematopoiesis and a myeloid predominance with a shift toward immaturity. Cytogenetic readings were normal.

Differential diagnosis of neutropenia

Congenital neutropenias

Newly detected neutropenia in a young patient, particularly one without known previously normal ANCs, raises the possibility of an occult congenital neutropenia syndrome (Table 1). These can be divided into pure neutropenic syndromes and congenital syndromes that include neutropenia as a component of their phenotypes. Of the pure neutropenic syndromes, benign familial, and constitutional

neutropenia are universally mild and do not lead to infectious sequelae, whereas patients with severe congenital neutropenia (SCN) have extremely low neutrophil counts or frank agranulocytosis, leading to chronic, severe infections.

Constitutional or ethnic neutropenia is characterized by mild, chronic neutropenia, usually with an ANC >1000 in a patient with no history of recurrent infections. Constitutional neutropenias are more common in patients of certain ethnic backgrounds, particularly those of Mediterranean and African descents.[1,2] Neutropenia in populations of African origin is linked to polymorphisms in the Duffy Antigen Receptor Complex (*DARC*) gene,[3] but the mechanism by which the Duffy-negative phenotype is linked to neutropenia is unknown, as is the extent to which DARC polymorphisms may be linked to constitutional neutropenia in other ethnic groups. In the vignettes described here, Patient 1 should be diagnosed with constitutional/ethnic neutropenia and not be subjected to further workup. Extensive evaluation of a healthy patient of African descent with an ANC in this range, even in the absence of a past history of CBC panels, is consistently uninformative.

Benign familial neutropenia is phenotypically similar to constitutional neutropenia but, although clearly hereditary, it is not linked to a particular ethnic group.[4] The genetic basis is unknown, although there is an evolving interest in whole-genome or whole-exome sequencing of affected individuals to help identify novel risk loci.

SCN is a group of inherited disorders characterized by agranulocytosis and recurrent, severe infections that begin during infancy.[5] Although the disease was formerly almost uniformly fatal in early childhood, its prognosis has been dramatically improved by the routine administration of granulocyte-colony stimulating factor (G-CSF).[6] At the same time, all subtypes of SCN carry a 10% to 30% lifetime risk of developing acute myelogenous leukemia.[7,8] AML is frequently associated with a truncation mutation of the G-CSF receptor, although how this contributes to pathogenesis is unclear.[9-11] Whether routine administration of G-CSF in these patients increases their risk of AML remains controversial.[12]

SCN is a heterogeneous syndrome, caused by inherited mutations in several neutrophil-specific genes, most commonly the primary granule protein gene neutrophil elastase (*ELANE*),[13-15] or the mitochondrial gene *HAX1*,[16] as well as a variety of rarer affected genes. SCN is uniformly diagnosed in infancy so it will not be discussed here further; several recent reviews detail the current understanding of the molecular pathogenesis of the syndrome.[17-19] The main significance of SCN here is that many adult patients present to the hematologist having read about SCN, and the consultant's role is to reassure the patients that they do not have one of these syndromes and are not at risk of developing acute leukemia.

Cyclic neutropenia (CN) is a rare congenital disease characterized by episodes of self-limited neutropenia that recur every 2 to 5 weeks.[20,21] The cycles are of varying length but are very consistent within each patient. The syndrome is usually of mild severity, although some patients can develop infections or oral ulcers during their neutrophil nadir. Unlike SCN, there is no increased risk of developing AML. Cyclic neutropenia is an autosomal dominant syndrome that, like autosomal dominant SCN, has been shown to result from mutations in *ELANE*.[22] Intriguingly, these mutations are not necessarily distinct: at least one kindred has been described in which some siblings had SCN and others with the same *ELANE* mutation had cyclic neutropenia.[23] How these identical mutations lead to such divergent phenotypes has not been elucidated. Because of its milder phenotype, cyclic neutropenia is often diagnosed in adulthood.

Table 2. Drugs associated with neutropenia or agranulocytosis

Class	Drug	Frequency reported	Nature of reaction
Antibiotics	Semisynthetic penicillins (amoxicillin, ampicillin*)	Int	Both
	Cephalosporins	Int	Both
	Vancomycin	High	Both
	Macrolides	Low	Neutropenia
	TMP-SMX*	High	Agranulocytosis
	Dapsone*	High	Agranulocytosis
	Chloramphenicol	High	Agranulocytosis
Antifungals	Amphotericin	Low	Neutropenia
	Flucytosine	Low	Agranulocytosis
Antimalarials	Chloroquine	Low	Agranulocytosis
	Quinine	Int	Agranulocytosis
Antiinflammatory agents	Ibuprofen*	Low	Agranulocytosis
	Diclofenac*	Int	Agranulocytosis
	Sulfasalazine*	High	Agranulocytosis
	Gold salts		Agranulocytosis
Antithyroid drugs	Methimazole*	High	Agranulocytosis
	Propylthiouracil	Int	Agranulocytosis
Psychotropic agents	Clozapine*	High	Agranulocytosis
	Phenothiazines (chlorpromazine)	Int	Agranulocytosis
	Tricyclic agents (amitriptyline*)	Low	Agranulocytosis
Antiepileptics	Carbamazepine*	Low	Neutropenia
	Phenytoin*	Int	Agranulocytosis
	Valproate	Low	Neutropenia
	Ethosuximide	Low	Neutropenia
Cardiovascular drugs	Antiarrhythmic agents (procainamide,* flecainide*)	High	Agranulocytosis
	ACE inhibitors	Int	Agranulocytosis
	Propranolol	Low	Agranulocytosis
	Digoxin*	Int	Agranulocytosis
	Ticlopidine	High	Agranulocytosis
Diuretics	Thiazides*	Low	Neutropenia
	Furosemide	Low	Neutropenia
	Spironolactone*	Low	Agranulocytosis
	Acetazolamide	Low	Neutropenia
Other	Deferiprone*	Int	Agranulocytosis
	Levamisole	Int	Agranulocytosis
	Rituximab	Int	Agranulocytosis

Excludes drugs for which neutropenia is an expected side effect (eg, chemotherapy). Int, intermediate.

"Frequency reported" refers to the number of case reports in recent systematic reviews for each drug, but is not always normalized to the frequency with which each drug is prescribed and thus may not accurately represent the true risk associated with these drugs.[37]

"Nature of reaction" means that all of the drugs in this table have been reported to be associated with agranulocytosis, but some more frequently cause dose-related neutropenia in clinical practice.

*Denotes drug for which specific attributable risk has been reported in either case-controlled studies or studies normalized to the prescription rate.

Neutropenia also occurs as part of the spectrum of a number of congenital syndromes, including Shwachman-Diamond syndrome,[24] Fanconi anemia,[25] dyskeratosis congenita,[26,27] Chediak-Higashi syndrome,[28] myelokathesis,[29,30] Griscelli syndrome II,[31] and cartilage-hair hypoplasia.[32] Although neutropenia may arise in young adults with these syndromes, the primary immunodeficiency is usually diagnosed in childhood, and they will not be discussed further.

Acquired neutropenias are more common than congenital neutropenias. They can be seen after infections or after exposures to certain drugs, in the setting of autoimmunity, nutritional deficiency, or hypersplenism, or as a consequence of a hematologic malignancy.

In addition, a significant number of patients with neutropenia have chronic idiopathic neutropenia.

Postinfectious neutropenia is most commonly seen in children after viral infections. It can be caused by almost any viral infection, though it is most commonly seen after varicella, measles, rubella, influenza, hepatitis, Epstein-Barr virus, or HIV infection. Although most are self-limited, neutropenia after Epstein-Barr virus[33] and HIV[34] infection can sometimes be prolonged. Bacterial infections are a rarer cause of significant neutropenia, with notable exceptions including *Brucella*, rickettsial, and mycobacterial infections. In addition, severe sepsis from nearly any pathogen can result in neutropenia; this is most commonly seen in infants and the elderly, is thought to result from exhaustion of marrow granulocyte reserves, and carries a grave prognosis.[35]

Drugs and toxins are among the most common causes of acquired neutropenia.[36] Neutropenia has been reported in association with an extensive array of medications (Table 2). However, certain common offenders bear specific recognition. The most obvious are chemotherapeutic drugs, many of which cause bone marrow suppression as an expected consequence of their mechanisms of action. The antipsychotic agent clozapine, the antiplatelet drug ticlopidine, and the antiinflammatory drug sulfasalazine all have well-known associations with idiosyncratic agranulocytosis.[37] In the case of clozapine, agranulocytosis appears to result from the toxic effect of a drug metabolite that may also have an impact on the marrow stroma; this may cause a somewhat more prolonged neutropenia than is usually seen in drug-induced agranulocytosis.[38] Other drugs commonly implicated in neutropenia include phenothiazines (eg, chlorpromazine),[39] semisynthetic penicillins (eg, ampicillin) and cephalosporins,[40] thionamides (methimazole, propylthiouracil), and nonsteroidal antiinflammatory drugs.[41] It is important to note that the true potential of each drug to cause neutropenia may not be accurately reflected by the incidence calculated from case reports, because these are not usually normalized to the prescription rate of the drugs. In the few studies that have corrected for the rate of prescription, a handful of drugs (clozapine, methimazole, sulfasalazine, trimethoprim-sulfamethoxazole, and β-lactam antibiotics as a class) have shown the highest odds ratios for causing serious neutropenia.[36,37]

One must differentiate mild, dose-related neutropenia from idiosyncratic agranulocytosis. The true incidence of mild dose-related neutropenia can be difficult to estimate accurately for any drug, because most systematic reviews have focused exclusively on agranulocytosis.

However, the distinction is clinically important, because patients with drug-induced agranulocytosis frequently present with acute febrile illness or sepsis, whereas most cases of drug-induced neutropenia in the outpatient setting are mild, dose-related, and of minimal concern. Patients with mild neutropenia can typically continue treatment if the drugs are otherwise improving their symptoms. In contrast, patients who develop early neutropenia while taking drugs known to cause agranulocytosis at high rates (eg, clozapine, methimazole) should discontinue taking the drug immediately.

Diet and substance use

Patients with severe caloric malnutrition (eg, patients with anorexia nervosa) can be leukopenic, but this is usually mild. Patients with folate or vitamin B_{12} deficiency can be neutropenic, but this rarely occurs without concomitant macrocytosis and pancytopenia. Copper deficiency, a less common cause of leukopenia, has some clinical features that overlap with those of B_{12} deficiency and is most

commonly found in patients who have undergone certain types of gastric bypass surgery.

Autoimmune neutropenia can occur either in isolation[42] or in association with systemic autoimmune diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). It is caused by autoantibodies directed at specific neutrophil antigens.[43] Most of these antigens are surface glycoproteins, including FcγIIIb, CD177, CD11a, and CD11b.[44]

Neonatal alloimmune neutropenia is characterized by perinatal transient neutropenia, caused by the passage of antineutrophil antibodies to the fetus via the placenta.[45] These antibodies are maternally derived as a result of sensitization to paternal antigens and can be detected in normal pregnant women (1% of the population in some studies), the majority of whose infants never develop neutropenia. The disorder is transient and treatment is seldom required, but the neutropenia responds to G-CSF in prolonged cases or in cases complicated by serious infections.

Primary autoimmune neutropenia usually occurs during the first year of life. As the name implies, it manifests without other signs or symptoms of an underlying autoimmune disorder.[46] Neutropenia can be moderate to severe and complicated by serious infections. Although the disease is usually self-limited and spontaneously remits within 2 years in about 95% of cases, prophylactic antibiotics and treatment with G-CSF during the neutropenic period are often necessary.[47]

Secondary autoimmune neutropenia is seen primarily in adults and usually occurs within the context of systemic autoimmune disease. Autoimmune neutropenia is frequently a benign disorder that manifests as mild neutropenia, and in the setting of systemic autoimmune disease is a manifestation of the activity of the underlying disorder. It seldom needs treatment, but it often responds to either steroids or intravenous immunoglobulin when they are used to treat other concomitant autoimmune symptoms.[48] As with other types of neutropenia, the indication for treatment is based on the presence of recurrent infections in the setting of an ANC <500. A special case is neutropenia in association with large granular lymphocytes, which is typically more severe (discussed later).

Felty syndrome refers to the triad of RA, splenomegaly, and neutropenia.[49] It is classically associated with long-standing and deforming RA; because of the widespread use of effective disease-modifying agents, Felty syndrome is substantially less common today than it has been in the past. Patients with Felty syndrome often have substantial morbidity from serious bacterial infections. Effective treatment of the underlying RA usually improves the neutropenia,[50] although G-CSF can be helpful in refractory cases.[51]

Large granular lymphocyte leukemia (LGL)-associated neutropenia shares many features with Felty syndrome, including an association with RA,[52] frequent splenomegaly, and a strong association with HLA-DR4.[53] However, as the name implies, LGL-associated neutropenia occurs in the context of a monoclonal population of large granular lymphocytes, whereas the lymphocytes in Felty syndrome are polyclonal or oligoclonal. In the setting of RA, LGL neutropenia is associated with T-cell LGL. The strong association of RA-related LGL and Felty syndrome with HLADR4 positivity has led to the suggestion that the 2 diseases are part of a single disease spectrum.

LGL-associated neutropenia is often associated with severe neutropenia and usually requires therapy. It is quite responsive to immunosuppression with methotrexate or cyclophosphamide. Patients also respond to G-CSF; however, because mature neutrophils bear G-CSF receptors, G-CSF therapy is often associated with an acute flare of joint symptoms.

In the non-RA population, LGL can be either T-cell LGL or natural killer (NK)-cell LGL. Although T-cell LGL is associated with severe neutropenia that usually requires treatment, it rarely leads to serious lymphoma-associated manifestations. By contrast, NK-cell LGL is typically an aggressive disease that lacks an association with either neutropenia or rheumatologic disease.[54]

Neutropenia is seen quite commonly in SLE (occurring in as much as 50% of patients in some case series).[48] It tends to track with disease activity, with neutrophil counts often dropping during disease flares. However, it has little overall impact on the course of the disease, and the infectious complications of SLE tend to correlate better with the degree of immunosuppressive therapy than with the degree of neutropenia.

In this study, Patient 2 was diagnosed with a form of immune neutropenia, based on his prompt (and subsequently complete) response to low-dose methotrexate. One would predict that he would have detectable LGL in his blood and bone marrow; interestingly, however, these were both negative in this patient. This suggests that one should consider immune neutropenia in the differential diagnosis of severe acquired neutropenia, even in the absence of a specific syndrome.

Chronic idiopathic neutropenia

Neutropenia that is acquired in adulthood but eludes a specific diagnosis is termed *chronic idiopathic neutropenia* (CIN). It is a diagnosis of exclusion that can only be made after a thorough and unrevealing search for other causes, including negative testing for autoimmune disease and nutritional deficiency and a normal bone marrow examination with normal cytogenetics. Its pathogenesis is unknown. Studies from the island of Crete, where neutropenia is quite common, have shown an association between neutropenia and myeloid hypoplasia, with a selective decrease in CD34$^+$/CD33$^-$ progenitors or with increased production of TNF-α.[55,56] However, the neutropenia in that population is quite mild, with ANCs usually no lower than 800, and may reflect at least a component of constitutional neutropenia. This mild phenotype is distinct from another subset of patients with CIN who have profound neutropenia (ANC <200). Despite their very low neutrophil counts, these patients usually follow a benign clinical course, although some may require G-CSF for recurrent infections. There are virtually no data concerning these patients in the literature and, as noted, the pathogenesis of their neutropenia remains a mystery.

In the vignettes described earlier, Patient 3 had chronic idiopathic neutropenia. This puzzling syndrome requires further study to elucidate its pathogenesis. Nevertheless, even in the absence of an explanation for the disease, the patients can be reassured that it is a benign syndrome that rarely needs therapy. In patients with recurrent infections, G-CSF, usually at low intermittent doses, controls the disease.

Initial triage of the neutropenic adult

Before initiating an evaluation of newly discovered neutropenia in an adult patient, clinicians should consider a fundamental question: Is the patient acutely ill? Evaluation and treatment of an acutely ill patient not previously known to be neutropenic is a medical emergency (Figure 1). Patients are progressively at greater risk of serious infections with worsening neutropenia, with patients whose ANC is <500 at the greatest risk. Such patients who also have a fever >100.4°F should be admitted immediately to the hospital. After obtaining appropriate cultures, they should then be started on

Figure 1. Algorithm for the evaluation and treatment of adult patients with neutropenia.
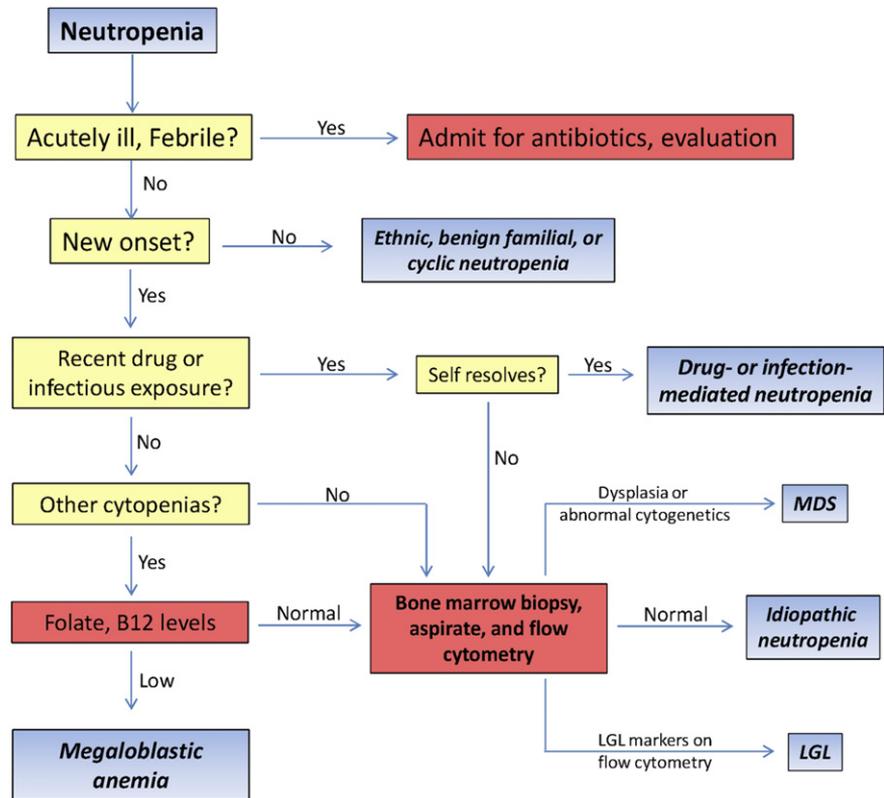
intravenous antibiotics that empirically cover *Pseudomonas aeruginosa* and other gram-negative bacteria. Patients with less severe neutropenia may still warrant hospitalization and empiric antibiotics if their presentation suggests a serious infection, and clinicians should recognize that what appears to be mild or moderate neutropenia may be an early point on a downward curve toward severe neutropenia or agranulocytosis.

Neutropenia discovered in the setting of acute illness is immediately concerning, particularly if the symptoms are associated with new recurrent infections or symptoms suggesting an underlying hematologic or rheumatologic disorder. On the other hand, neutropenia discovered on a routine blood count in an otherwise healthy individual is usually benign, although additional evaluation must always be considered before making that determination.

Outpatient evaluation of neutropenia

The evaluation of neutropenia in the outpatient referral population may lack the urgency of an inpatient evaluation but is often considerably more challenging. Evaluation should begin with a careful history. Younger patients younger than 30 to 40 years of age (as with Patient 1) may have no prior CBC panels for comparison, raising the possibility of an inherited disorder modest enough to have escaped detection during childhood, such as familial or constitutional neutropenia. Such inherited conditions are less likely to present late in adulthood, because older adults are more likely to have prior CBC panels for comparison, suggesting that most neutropenia detected in older adults is acquired.

The pattern of recent or recurrent infections may help define both the duration and clinical significance of neutropenia. Onset of recurrent infections in a patient who previously enjoyed good health, such as with Patient 2, can help pinpoint when the neutropenia began and also give insight into whether it reflects a serious illness. Recurrent infections in patients with chronic neutropenia are uncommon unless the ANC is <500/μL and are usually seen only if the ANC is <200/μL. Infectious syndromes of particular importance are pneumonia, sinusitis (particularly if there is evidence of bacterial involvement, with fevers and thick, purulent nasal discharge), frequent dental caries, and skin/soft tissue infections. Fungal infections and severe viral infections, both of which are more related to defects in adaptive immunity, are less common. Otitis media and recurrent oral ulcerations, especially those occurring since childhood, suggest lifelong neutropenia and in an otherwise healthy person support a diagnosis of chronic idiopathic neutropenia.

Other aspects of the history should include an assessment of ethnic background to determine the likelihood of constitutional neutropenia. A dietary history should be taken, although as stated before, most of the common deficiencies that cause cytopenias (eg, vitamin B_{12}, folate) cause pancytopenia rather than isolated neutropenia. Copper deficiency should be considered in patients who have a history of significant gastric surgery.

In otherwise healthy patients with incidental neutropenia, the physical examination should focus on examination for adenopathy or splenomegaly, as well as specific signs of active or prior infection, such as healing skin ulcers or aphthous ulcers. There are few other specific physical examination findings that are helpful.

All patients with neutropenia should have a CBC panel with manual smear done and preferably reviewed by a hematologist or hematopathologist, as well as chemistry panels and measurements of liver and renal function. For patients with minimal or no symptoms of infection or other illnesses, serial CBC panels over a period of days or weeks may establish a trend in the neutrophil count. If CN is

suspected, twice weekly blood counts for 4 to 6 weeks may establish a cyclic pattern (alternatively, the diagnosis can be made by sequence analysis of the ELANE gene, which is mutated in nearly 100% of patients with CN). Alternatively, a steadily declining ANC is not characteristic of most benign neutropenic syndromes and suggests an underlying infectious, autoimmune, or neoplastic cause that requires further evaluation.

ANA and rheumatoid factor are good initial screening tests for diagnosing systemic rheumatologic disease, and the erythrocyte sedimentation rate and C-reactive protein number can be useful for detecting underlying inflammation. Even in the absence of obvious lymphocytosis or a history of autoimmune disease, all patients should have peripheral blood flow cytometry to evaluate for LGL. Finally, all patients with neutropenia should have an HIV test done if one has not been performed recently.

One question that arises is whether to test for the presence of antineutrophil antibodies, which can be found in some cases of both autoimmune disease–associated or idiopathic neutropenia. Although these tests are very useful in evaluating neonatal neutropenia, they are rarely helpful in diagnosing adult patients. Furthermore, although there are a number of commercially available assays for antineutrophil antibodies, several pitfalls limit their applicability in clinical practice. First, there is a relatively high rate of false-positive results because of the high concentration of Fc receptors on neutrophils, the tendency of neutrophils to spontaneously fluoresce, and the tendency of neutrophils to spontaneously aggregate in vitro. Second, even if the positive predictive value of the test was assured to be high, the clinical significance remains unclear. A substantial portion of the normal population can be shown to have circulating antineutrophil antibodies, such that detection of antibodies does not necessarily imply pathogenicity. Finally, a reliable correlation between the detection of antineutrophil autoantibodies and response to treatment with immune-suppressive therapies has never been demonstrated. Thus we rarely encounter a circumstance in which antineutrophil antibodies are helpful, and rarely, if ever, check them in the scope of our usual clinical practice.

Bone marrow aspiration and core biopsy should be considered in all patients with unexplained neutropenia to establish that there are no signs of dysplasia, cytogenetic abnormalities, or involvement by a neoplastic process such as leukemia, lymphoma, or myeloma. However, in patients with a long history of mild isolated neutropenia, the results of bone marrow aspiration and biopsy are nearly uniformly inconclusive, deeming the procedures probably unnecessary. It should also be noted that for both case vignettes described before in which bone marrow examination was performed, the study did little to aid in making a diagnosis. In particular, marrow examination is not necessary to diagnose lymphoma or LGL, which can both be detected by flow cytometry of the peripheral blood (marrow infiltration with lymphoma sufficient to cause neutropenia should be detectable by peripheral blood flow). Despite this, many patients with chronic neutropenia undergo repeated bone marrow examinations despite little change in their clinical circumstances. Consequently, in patients in whom we decide to perform blood marrow examination, we advise them not to have repeated studies unless there is a dramatic change in their peripheral counts. When obtained, the aspirate should be sent for routine pathological examination, as well as flow cytometry for leukemia and lymphoma markers, and cytogenetics.

Management of the neutropenic patient

The majority of the disorders discussed here fall into 2 groups: those that require no treatment (constitutional neutropenia, familial neutropenia, most cyclic neutropenias), and those secondary disorders whose management is outside the scope of this review. We will instead focus our comments on 2 points.

Autoimmune neutropenia

Autoimmune neutropenia, as in the case of Patient 2, should be suspected in a patient with a steadily declining ANC in whom other causes of neutropenia (eg, infection, drugs/toxins, leukemia/myelodysplastic syndrome) have been ruled out. As discussed before, autoimmune neutropenia is a clinical diagnosis, and assays for antineutrophil antibodies are usually unhelpful. Treatment should be considered for patients who have developed infectious complications from their neutropenia, though if possible it should be deferred until those infections have cleared. LGL-associated neutropenia responds well to low-dose methotrexate or cyclophosphamide.[57,58] Interestingly, despite the fact that it is a T cell–mediated disease, autoimmune neutropenia may also respond to rituximab.[59] Most patients will also respond to G-CSF, although in the setting of RA, this may cause an acute exacerbation of joint symptoms.

When to use growth factors

We typically reserve G-CSF for patients with recurrent or severe infections or symptomatic mucosal erosions or skin infections. In particular, we reiterate that patients with CIN and many familial neutropenia syndromes usually have a benign course, even with profoundly low ANCs, and we thus caution against basing the initiation of G-CSF on the ANC alone. When initiating cytokine therapy, we find that pegylated G-CSF (pegfilgrastim, Neulasta) causes more severe and prolonged bony pain, so we prefer to use G-CSF (filgrastim, Neupogen). We generally use the minimum dose and frequency to maintain a neutrophil count in a range to prevent symptoms. This can usually be accomplished by maintaining an ANC >250 to 300 and can often be maintained with dosing one to three times weekly. Although there is some concern that chronic G-CSF increases the risk of leukemia in children with SCN, it is not clear whether this is a direct consequence of G-CSF use or is in fact a consequence of the extended life expectancy of SCN patients, which has unmasked an inherent risk of leukemia. Regardless, there is no evidence for any such risk in adults with chronic neutropenia who require long-term growth factor support.

Authorship

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