Why is My Patient Neutropenic?

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NEUTROPHIL OVERVIEW

Neutrophils (also called granulocytes) are produced exclusively in the bone marrow during normal conditions. Approximately 10^{12} neutrophils are produced per day in the bone marrow and then stored in the marrow until prompted for release by chemokines, cytokines, microbial products, or other mediators of inflammation. Once released into the bloodstream the average half-life of neutrophils is 6 to 8 hours. Circulating neutrophils, the ones reported in a standard complete blood count (CBC), account for only 2% to 3% of all neutrophils. Clearance occurs in the liver, spleen, or bone marrow and occurs through macrophage phagocytosis of aged or apoptotic neutrophils. The local production of inflammatory cytokines and chemokines leads to neutrophil attachment to the vascular endothelium and the subsequent transmigration of neutrophils into tissue. The migration of neutrophils into tissue is a key component of the innate immune system, as evident by the increased risk of infections seen in the setting of neutropenia.

NEUTROPENIA

Neutropenia is defined as an absolute neutrophil count (ANC) less than 1500 cells/μL; it may be mild (ANC 1000–1500 cells/μL), moderate (500–1000 cells/μL), or severe (<500 cells/μL) (**Table 1**). In general, infection risk increases with ANC less than 1000 cells/μL; however, the risk for infections varies depending on the cause of neutropenia. For example, patients with neutropenia and acute leukemia seem to have a high risk for overwhelming infection in the setting of neutropenia, particularly in cases with ANC less than 500 cells/μL.[1] Therefore, the context in which neutropenia occurs must be considered because some causes of neutropenia, namely ethnic neutropenia and chronic idiopathic neutropenia (CIN), have few overall infection risks.

Table 1 Severity of neutropenia		
	ANC	Risk of Infection
Mild neutropenia	ANC <1500 but >1000	Mild
Moderate neutropenia	ANC <1000 but >500	Moderate
Severe neutropenia	ANC <500 but >200	Severe
Agranulocytosis	ANC <200	Severe

DIAGNOSTIC WORKUP

Initial workup consists of a CBC, with a differential count to evaluate the severity of the neutropenia. A full history is also essential to determine race, ethnicity, new medications (including over-the-counter and complementary medications), and potential infectious exposures. Review of systems should focus on fevers, chills, night sweats, weight loss, excess bleeding or bruising, or recurrent infections. A comprehensive physical examination should be performed, with a focus on an examination for signs of infection, hepatosplenomegaly, and lymphadenopathy. After this examination, a detailed review of the peripheral smear should follow, to look for neutrophil abnormalities such as Döhle bodies (infection), immature neutrophil precursors (infection, myelodysplasia, myelopthisis), hypoplastic changes in the neutrophils (myelodysplasia), hyperlobulation (nutritional deficiencies), and white cell inclusions (eg, anaplasmosis (Fig. 1), bartonellosis). Review of red cell morphology on peripheral smear may also offer clues to the cause of neutropenia because dacrocytes (teardrop cells) and nucleated red cells (myelodysplasia, fibrosis, myelopthisis) in addition to red cell inclusions (eg, babesiosis, malaria) may all be seen in disease states associated with neutropenia.

Additional routine blood work should include:

- Reticulocyte count
- Lactate dehydrogenase
- Erythrocyte sedimentation rate
- Rheumatoid factor/anticyclic citrullinated protein antibody
- Antinuclear antibodies
- Thyroid-stimulating hormone
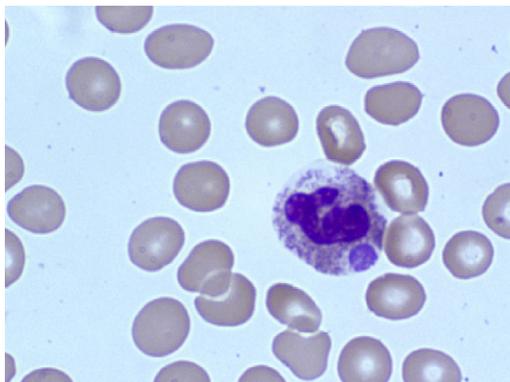
Fig. 1. Neutrophil with an intracellular morula in a patient with anaplasmosis.

- Human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay (ELI-SA) test with confirmation by Western blot
- Vitamin B_{12} levels
- Folate levels.

In cases in which diarrhea is present, stool samples should be checked for the presence of fecal leukocytes and cultured for *Shigella* and *Salmonella*. If tick-borne illnesses are part of the differential diagnosis, then an ELISA for *Borrelia burgdorferi*, the causative agent of Lyme disease, should be ordered and, if positive, the result should be confirmed by Western blot. If babesiosis is suspected, *Babesia* immunofluorescent antibody (IFA) and polymerase chain reaction (PCR) tests should be ordered. *Anaplasma* infection should be evaluated, if needed, by IFA, ELISA, or PCR tests. The granulocyte agglutination test or granulocyte immunofluorescence test for antigranulocyte antibodies to evaluate potential autoimmune neutropenic syndromes may be considered. Bone marrow aspirate and biopsy should be reserved for those cases in which there is a high suspicion for malignancy, either hematologic or metastatic solid tumor.

CAUSES

The most common causes of neutropenia are shown in **Boxes 1–3**.

ETHNIC VARIATION

Ethnic neutropenia has been described in persons of African, African American, Yemenite Jewish, West Indian, and Arab Jordanian ancestry.[2,3] In the United States, the prevalence of neutropenia (ANC <1500 cells/μL) amongst African Americans is 4.5%, whereas it has been reported at 0.79% and 0.38% in whites and Mexican-Americans, respectively.[2] The pathophysiology in ethnic neutropenia seems to be a decrease in the number of neutrophil precursors within the bone marrow. However, there is no decrease in the functionality of the neutrophils.[4] Ethnic neutropenia is a benign process that carries no increased risks for infections but should be considered early in the initial diagnostic workup to prevent unnecessary testing. Recently, the role of ethnic neutropenia has been addressed in patients receiving chemotherapy, because most clinical trials withhold chemotherapy in the setting of an ANC less than 1500 cells/μL. Hsieh and colleagues[2] make the case that chemotherapy can be administered with granulocyte colony-stimulating factor (G-CSF) support, if appropriate, in patients with ethnic neutropenia at ANC of 500 to 1500 cells/μL.

CONGENITAL NEUTROPENIA

The hematologist who treats adults should also be familiar with congenital forms of neutropenia (see **Box 2**). Cases can be mild and therefore not diagnosed until patients reach their adult years and have more regular blood work performed. Moreover, patients with severe forms of congenital neutropenia are living longer and require transitions from pediatric hematologists to their adult counterparts. The 2 most common forms of congenital neutropenia, cyclic neutropenia and severe congenital neutropenia (SCN, or Kostmann syndrome), are reviewed here with other causes of congenital neutropenia.

Cyclic Neutropenia

Typically, in cyclic neutropenia a family history is important because the condition occurs through autosomal-dominant inheritance, although sporadic cases have

> **Box 1**
> **Causes of neutropenia**
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> 1. Ethnic variations
> 2. Immune-related
>   a. Primary immune neutropenia
>   b. Secondary immune neutropenia
>   i. Felty syndrome (FS)
>   ii. Systemic lupus erythematosus (SLE)
>   iii. Rheumatoid arthritis (RA)
> 3. Infectious
>   a. Sepsis
>   b. Parasitic
>   c. Viral
>   d. Bacterial
> 4. Malignancy
>   a. Acute leukemia
>   b. Myelodysplastic syndrome (MDS)
>   c. Myelophthisis
>   d. Large granulocytic lymphocytic leukemia
> 5. Medication
>   a. Antibiotics
>   b. Cardiac
>   c. Anticonvulsants
>   d. Psychiatric
>   e. Antiinflammatory
>   f. Hypoglycemics
>   g. Antineoplastic agents
> 6. Mechanical
>   a. Splenomegaly
> 7. Nutritional deficiencies
>   a. Vitamin B_{12} (cobalamin)
>   b. Folic acid
>   c. Copper
> 8. Other
>   a. Hypothyroidism/hyperthyroidism

been reported. The neutrophil count cycles over an approximately 21-day period. Patients commonly develop oral ulcerations, fevers, cervical lymphadenopathy, and skin infections during neutrophil nadir periods, but severe infections are usually not seen. The disorder is secondary to a mutation in the neutrophil elastase gene that leads to increased apoptosis in neutrophil precursors.[5] Treatment, if required, is

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Box 2
Causes of congenital neutropenia

1. Severe congenital neutropenia (SCN)
2. Cyclic neutropenia
3. WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome
4. Shwachman-Diamond syndrome
5. Barth syndrome
6. Pearson syndrome
7. Glycogen storage disease type 1B
8. Cartilage-hair hypoplasia
9. Dyskeratosis congenita

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centered on G-CSF with good overall results. The level of neutropenia sometimes improves with age.[6]

Severe Congenital Neutropenia (Kostmann Syndrome)

Initially described by the Swedish physician Rolf Kostmann in 1956 in a cohort of children who presented with agranulocytosis and severe infections. SCN was, at first, believed to occur through autosomal-recessive inheritance. However, autosomal-dominant inheritance and sporadic cases of SCN have also been reported. Like cyclic neutropenia, mutations in the neutrophil elastase gene have been found in patients with SCN, although bone marrow biopsy shows maturation arrest at the promyelocyte stage. However, the role of these mutations remains unclear because they were found in a subgroup of patients with SCN but were also found in phenotypically normal family members.[5] HAX1 gene mutations have been associated with autosomal-recessive forms of SCN,[7] whereas ELA2 mutations are commonly found in autosomal-dominant and sporadic cases of the disease.[8] More recently, a mutation in the G6PC3 gene has also been shown to result in SCN.[9] More than 90% of the patients respond to G-CSF administration. Long-term complications include a risk for transformation to myelodysplasia or leukemia in 22% of patients. This transformation has been unmasked now that patients live longer because of G-CSF therapy.[10] Vasculitis, splenomegaly, and osteoporosis frequently occur in this patient population.[11]

IMMUNE-RELATED NEUTROPENIA

Immune causes of neutropenia are secondary to circulating antibodies binding to and destroying peripheral neutrophils. Autoimmune neutropenia (AIN) can be either primary, when no clear underlying cause is present, or secondary, when it is associated with an underlying autoimmune condition. Disease states seen with secondary AIN are typically RA and SLE, although other autoimmune diseases, malignancies, infection, and drugs may also be associated.

Primary AIN

The diagnosis of primary AIN is based on the presence of antigranuloctye antibodies and the absence of a potential underlying disease-specific cause, as outlined in the section on secondary AIN. Primary AIN is usually seen in children younger than 2 years of age, and common associated infections include skin, upper respiratory, and ear infections. Most patients with AIN have antibodies that recognize antigens on the

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Box 3
Infectious causes of neutropenia

1. Sepsis
2. Parasitic
    a. Malaria
    b. Leishmaniasis (kala-azar)
    c. Babesiosis
3. Viral
    a. HIV
    b. Human herpesviruses
        i. Herpes simplex virus 1 and 2
        ii. Varicella zoster virus
        iii. Epstein-Barr virus
        iv. Cytomegalovirus (CMV)
        v. Roseolovirus (sixth disease)
    c. Parvovirus B19 (fifth disease)
    d. Hepatitis A, B, and C virus
    e. Measles
    f. Rubella
4. Bacterial
    a. *Shigella*
    b. *Salmonella* (typhoid fever)
    c. Zoonotic diseases (tularemia, brucellosis)
    d. Anaplasmosis
    e. Lyme disease
5. Mycobacterial
    a. *Mycobacterium tuberculosis*
    b. *M avium*

IgG Fc receptor IIIb. In terms of clinical course, primary AIN is usually self-limited. In severe cases of primary AIN in which there is persistent infection or when surgery is required, G-CSF, steroids, or intravenous immunoglobulin can be used, with response rates of 100%, 75%, and 50%, respectively.[12]

Pure White Cell Aplasia

Neutropenia in which there are no neutrophil precursors present in the bone marrow alongside normal red blood cell and platelet precursors is termed pure white cell aplasia (PWCA). PWCA is a rare cause of neutropenia, for which only case reports are available. There seems to be an association with thymoma,[13] with treatment centered on thymoma removal along with immunosuppressive therapy such as rituximab and cyclosporine.[14,15] The mechanism of action is immune mediated by antibody development to neutrophil progenitor cells that spares pluripotent stem cells, erythroid precursors, and mature neutrophils.[16]

Secondary AIN

Systemic lupus erythematosus

Neutropenia has been reported in approximately 20% to 50% of patients with SLE.[17–19] The incidence of moderate to severe neutropenia is less; 1% to 5% of patients with SLE had ANCs less than 1000 cells/μL.[18] Associated findings in patients with SLE and moderate to severe neutropenia are use of medications known to cause neutropenia (ie, cotrimoxazole, phenytoin, and amoxicillin/clavulanic acid), immunosuppressive drugs, thrombocytopenia, and central nervous system involvement of SLE.[20] The mechanism by which neutropenia occurs in SLE is through antineutrophil antibody production, increased apoptosis of circulating neutrophils,[21] and a direct myelosuppressive effect by SLE on the bone marrow.[22,23] In terms of antibody production, 1 hypothesis is that anti-SSA (Ro) and anti-SSB antibodies either cross-react with neutrophil epitopes or bind directly to neutrophil antigens. In the case of anti-SSA, antibody binds neutrophils, activating complement fixation and neutrophil destruction.[24] Anti-SSB antibodies have been detected in the sera of patients with neutropenia and have been shown to increase neutrophil apoptosis.[25] The first step in treating SLE-associated neutropenia is to treat the SLE itself. Persistent moderate to severe neutropenia in a patient with well-controlled SLE warrants a closer look at potential offending medications as well as possible infectious causes, particularly when immunosuppression is present. G-CSF should be used in caution in patients with SLE because mild to severe disease flares have been described, including cases of irreversibly damaged renal function.[26]

Rheumatoid arthritis and felty syndrome

FS is a variant of RA associated with leukopenia, most often manifesting as neutropenia, splenomegaly, severe arthralgias, rheumatoid nodules, pulmonary fibrosis, and vasculitis. Laboratory findings associated with FS are increased levels of RF, hypergammaglobulinemia, and immune complexes in the blood.[27] Almost 90% of patients with FS are HLA-DR4+. This same high percentage is seen in patients with RA and large granular lymphocytic (LGL) leukemia, suggesting that these 2 diseases may represent 1 entity.[28] The primary treatment of FS is immunosuppression; however, care must be taken given the high rate of overwhelming sepsis in this patient population. Methotrexate, hydroxychloroquine, and intravenous immunoglobulin have been used with varying success. Rituximab does not have activity in FS. In cases of severe neutropenia, G-CSF can be used with the goal of an ANC greater than 1000 cells/μL but as in SLE-induced neutropenia the use of G-CSF has been associated with vasculitic flares and worsening arthralgias.[29]

Hyperthyroidism (Graves disease)

Hyperthyroidism has been shown to cause neutropenia, with improvement in neutrophil levels with correction of excess thyroid hormone production.[30] Both cell-bound and circulating antineutrophil antibodies have been found in the serum of patients with Graves disease, suggesting an underlying autoimmune process.[31]

Chronic idiopathic neutropenia

Patients without another clear cause for their neutropenia are frequently labeled with CIN. The clinical hallmarks of CIN are an acquired neutropenia with a relatively stable, suppressed neutrophil count without recurrent infections.

Full diagnostic criteria are as follows:

- ANC less than 1800 cells/μL in whites or less than 1500 cells/μL in individuals of African ancestry for greater than 3 months

- No clinical, serologic, or imaging evidence for another cause of neutropenia
- Absence of radiation exposures, chemical compound use, or drug intake associated with neutropenia
- Normal bone marrow karyotype
- No antineutrophil antibodies detected in the serum (a minimum of 2 methods such as the granulocyte agglutination and granulocyte immunofluorescence test should be used for confirmatory purposes).

Historically, this diagnosis served as one of exclusion, with no clear underlying pathophysiologic mechanism. Recently, however, new data have described CIN as a failure of the bone marrow microenvironment. Patients with CIN have increased inflammatory changes within the bone marrow through the presence of activated T cells as well as interferon γ, tumor necrosis factor α, Fas-ligand, and transforming growth factor $\beta1$ (TGF-$\beta1$).[8] Mesenchymal stem cells seem to play a role in the formation of the bone marrow microenvironment through the increasing production of TGF-$\beta1$.[32] The overproduction of TGF-$\beta1$ in turn suppresses interleukin 10, an antiinflammatory cytokine.[33] These changes lead to increased apoptosis within neutrophil progenitor cells.

DRUGS

Drug-induced neutropenia is a rare condition, with reports of 2 to 15 cases per million per year. However, it remains a common cause for neutropenia and should be considered at the outset in any patient presenting with neutropenia. The incidence increases with age, likely because older patients are exposed to more drugs than younger individuals. Almost all medication classes have been implicated; however, the major causes of drug-induced neutropenia include β-lactam antibiotics, cotrimoxazole, antithyroid medications, ticlodipine, neuroleptics such as clozaril, antiepileptics, and nonsteroidal antiinflammatory medications.[34] The onset of neutropenia and time to resolution of neutropenia are dependent on the drug involved.[35] Ten common causes of drug-induced neutropenia are outlined in **Table 2**.

Neutropenia secondary to medications is typically caused by either repeated exposure to the drug, resulting in myelosuppression, or through intermittent exposure, causing an immunologic phenomenon. Immune-mediated drug-induced neutropenia is most commonly seen in β-lactam antibiotics and antithyroid medications and is directly secondary to antibody production and subsequent neutrophil or neutrophil progenitor destruction. A bone marrow biopsy can be informative to define the duration of neutropenia. In scenarios in which no neutrophil precursors are present, recovery of neutrophils can take up to 14 days. However, in other settings, there is a picture of myeloid maturation arrest in which precursors are still present but mature neutrophils are absent. In this case, recovery takes 5 to 7 days.[34]

In a recent systemic review by Andersohn and colleagues that compiled all case reports of drug-induced neutropenia,[35] those with an ANC less than 100 cells/μL experienced higher rates of fatal complications than patients with ANC greater than 100 cells/μL. With regard to treatment, the first intervention is discontinuation of the suspected medication. The investigators also include data about the typical length of time culprit medications are taken before neutropenia occurs and the expected time for recovery once culprit medications are discontinued. Careful assessment of the risks for infection is necessary, with action taken if fevers develop. The role of growth factor support is less clear. Andersohn and colleagues show no statistically significant difference in the percentage of deaths in patients with drug-induced thrombocytopenia who were given growth factor support (5%) versus those who were not (6%). Therefore, in

Table 2
The 10 most common medications that cause drug-induced neutropenia as adapted from Andersohn et al.[35] All medications have at least 1 definite case report as a causative agent for neutropenia

Drug	Class	Definite Cases	Probable Cases	Duration of Exposure Before Neutropenia Onset (d)	Time to Neutrophil Recovery (d)
Dipyrone	Nonsteroidal antiinflammatory	6	5	2	10
Procainamide	Antiarrythmic	3	19	47	8
Quinidine	Antiarrythmic	3	4	35	4
Nafcillin	Antibiotic	1	4	22	8
Oxacillin	Antibiotic	2	4	22	4
Penicillin G	Antibiotic	4	7	25	4
Levamisole	Antirheumatic	2	6	60	10
Propylthiouracil	Antithyroid	1	10	36	10
Chlorpromazine	Antipsychotic	2	6	45	11
Clozapine	Antipsychotic	4	49	56	12

the setting of fevers and drug-induced neutropenia, broad-spectrum antibiotic coverage is warranted and growth factor support can be considered.[34,35]

Rituximab

Rituximab (Rituxan) is a chimeric anti-CD20 monoclonal antibody commonly used for the treatment of B-cell lymphomas and autoimmune conditions. Late-onset neutropenia (LON) has been described in which neutrophil counts decrease 3 to 4 weeks after the last rituximab infusion. The incidence has been reported as between 3% and 27% of patients, with those most at risk for LON being patients after autologous stem cell transplant, HIV-positive patients, and those patients who have received purine analogues such as fludarabine. The infection rate is close to 17%, and no clear mechanism of action has been defined.[36]

INFECTIONS
HIV

When evaluating the HIV-positive patient for neutropenia, it is paramount to first exclude indirect effects of HIV infection, such as medication effect from antiretroviral medications, opportunistic infections like CMV, or malignancy, before focusing on the role that HIV has on neutropenia (see **Box 3**). In terms of medications, the myelosuppressive effect of zidovudine (AZT) on the bone marrow was recognized in the late 1980s. The use of AZT has declined in the United States, although it continues to be one of the most common agents used in developing countries. In terms of frequency of drug-induced neutropenia in HIV, the primary culprit is AZT followed by trimethoprim/sulfamethoxazole and ganciclovir. In this patient population, chemotherapy- induced neutropenia was more likely to result in infection than other drug causes of neutropenia.[37] Opportunistic infections such as *M avium* complex (MAC), *M tuberculosis*, and *Histoplasma capsulatum* should be considered in the HIV patient with neutropenia in addition to the more common infections associated in neutropenia outlined later.

In terms of neutropenia frequency, the Women's Interagency HIV Study involving 1729 women found 44% of those with HIV with an ANC less than 2000 cells/μL, whereas 7% had an ANC less than 1000 cells/μL. During the 7.5-year follow-up period, 31% had at least 1 ANC less than 1000 cells/μL. Factors associated with neutropenia were a low CD4 count (<200 cells/μL) and high HIV viral load (>100,000 copies/mL). Conversely, an increased CD4 count (>500 cells/μL) and HAART (highly active antiretroviral therapy) were associated with correction of underlying neutropenia. No link between neutropenia and survival was found.[38] Another multinational study conducted in Africa, Asia, South America, the Caribbean, and the United States in which neutropenia was defined as an ANC less than 1300 cells/μL also found lower CD4 counts in addition to thrombocytopenia associated with neutropenia in newly diagnosed HIV-positive patients.[39] Low CD4 counts and the link to neutropenia have been described elsewhere.[40] The duration of neutropenia in patients with HIV is typically less than 2 weeks, with most individuals not developing infections.[41] The exact mechanism by which neutropenia occurs in patients with HIV is unclear. Studies have suggested direct effects of HIV causing increased apoptosis in neutrophils[42] as well as premature phagocytosis of bone marrow cells, which may account for the observed neutropenia. In addition, G-CSF levels in patients with HIV are lower than those without HIV.[43] In a randomized controlled trial, daily or intermittent filgrastim to keep the ANC greater than 2000 cells/μL was shown to decrease the number of episodes of severe neutropenia (ANC <500 cells/μL) or death in a statistically

significant manner compared with the control population who received G-CSF only for severe neutropenia.[44]

Other Viruses

A great deal of literature discusses the role of HIV in neutropenia. However, other notable viruses can be the cause of neutropenia. Many of these viruses such as human herpesvirus 6 and measles are typically seen in children. Others, like CMV, are typically seen in immunocompromised individuals but can occasionally be present in immunocompetent patients.

Bacterial

Sepsis is one of the most common bacterial causes of neutropenia and may be secondary to any bacteria type. Sepsis-induced neutropenia is caused by the consumption of neutrophils from the overwhelming infection. *Shigella* and *Salmonella* are potential causes, particularly in patients with a history of diarrhea. Typhoid fever secondary to *Salmonella* should be considered in patients with neutropenia and abdominal pain, particularly those who have recently traveled outside the United States to endemic areas. Zoonotic diseases such as tularemia and brucellosis may also present with neutropenia in patients with recent animal exposures.[45] In areas where tick-borne illnesses are abundant, anaplasmosis should be considered in the differential for patients who present with fevers and neutropenia. The neutropenia seen in anaplasmosis is through the direct infection of neutrophils with the gram-negative bacteria *Anaplasma phagocytophilum*.[45]

Parasites

Parasitic infections typically cause neutropenia via an indirect mechanism. In cases of malaria or visceral leishmaniasis, the resulting splenomegaly that develops through hemolysis leads to neutropenia.[45] Careful attention should be paid in the initial assessment to travel to areas where these diseases are endemic.

MALIGNANCY
LGL Leukemia

LGL leukemia can be either T-cell–mediated (T-LGL) (85%) or NK-cell–mediated (NK-LGL) (15%). LGL leukemia is most frequently seen in older patients, with an average age at diagnosis of 60 years. Neutropenia is seen in both T-LGL and NK-LGL leukemia, with case series reporting rates of 48% to 84% of patients with ANC less than 1500 cells/μL and 7% to 48% with ANC less than 500 cells/μL. Diagnosis is based on flow cytometry.[46] Clinical findings include splenomegaly in 25% to 50% of patients. Approximately half of patients require treatment because of either persistent neutropenia or anemia. No standard treatment modality exists, but immunosuppressive medications such as steroids, methotrexate, cyclophosphamide, and cyclosporine are commonly used. In observational data, cyclophosphamide seems to have the highest response rates.[47]

MDS

MDSs are a heterogeneous group of disorders characterized by ineffective hematopoiesis. Amongst types of MDS there is a variable rate of progression to acute myeloid leukemia. The hallmark of the disease is cytopenia, which typically manifests as isolated anemia, anemia in combination with neutropenia or thrombocytopenia, or pancytopenia. Cases in which neutropenia is present are more likely to be caused by refractory anemia with excess blasts than refractory anemia with ringed

sideroblasts.[48] Clues to the diagnosis are seen in the peripheral smear in the form of a macrocytic anemia and dysplastic changes in the neutrophils such as Pelger-Huet-like cells and hypogranulation. Diagnosis is confirmed through bone marrow biopsy and reveals a hyperplastic marrow with dysplastic findings in 1 or all lineages.

SUMMARY

Neutropenia is a common reason for a hematology consultation in the outpatient and the inpatient settings. The hematology consultant needs to obtain a full patient history, which includes details about the recent period during which neutropenia occurs, the patient's own history of neutrophil counts, recent changes in medications, and symptoms suggesting potential infections, rheumatologic disorders, or malignancies. Next, the hematology consultant should perform a complete physical examination, which can frequently yield important clues to the cause of the neutropenia. The hematologist provides the critical expertise in assessment of blood morphology through a careful analysis or the peripheral blood smear. Determination of the underlying cause for neutropenia is essential, because some causes such as ethnic neutropenia and CIN carry little risk for infection, whereas others, such as SCN, LGL leukemia, and MDS, are more likely to result in infections. However, data on the management of neutropenia remain scant and additional studies are needed.

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