22.3.8 Eosinophilia 5254 Peter F. Weller

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SECTION 22 Haematological disorders 5254 22.3.8 Eosinophilia Peter F. Weller ESSENTIALS Eosinophilia (eosinophil count >0.45 × 109/litre) is associated with some infections, some allergic diseases, and a variety of other condi- tions, sometimes neoplastic. Infectious diseases Parasitic diseases—eosinophilia is a characteristic feature of infection by multicellular helminth parasites (e.g. Strongyloides stercoralis) with diagnosis typically based on geographical/dietary history, serological tests, and examination of stool or tissues for parasite forms. Other diseases—eosinophilia can be caused by the fungal disease coccidioidomycosis, and modest eosinophilia (0.45–1.5 × 109/litre) may accompany retroviral infections such as HIV and HTLV-1. Allergic, immunological, neoplastic, and other disorders Common allergic diseases—asthma, rhinitis, and atopic dermatitis are associated with modest eosinophilia. Drug reactions—these are a frequent cause of eosinophilia, at times in reactions characterized by rashes and pyrexia. More severe reactions may also manifest with (1) pulmonary eosinophilia and lung infiltrates; (2) interstitial nephritis; (3) hepatitis; (4) myocarditis; (5) drug-induced hypersensitivity vasculitis; (6) gastroenterocolitis; and (7) drug-induced rash, eosinophilia, and systemic symptoms (DRESS syndrome). Other conditions—these include (1) eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss syndrome); (2) hyper-IgE syndromes—comprising recurrent staphylococcal abscesses, derma- titis, hyperimmunoglobulinaemia E, and eosinophilia; (3) chronic mye- loid leukaemia, acute myeloid leukaemia, and lymphoma; (4) a variety of pulmonary, skin, gastrointestinal, and endocrine diseases. Hypereosinophilic syndromes These are defined by (1) eosinophilia (>1.5 × 109/litre) sustained over a month, (2) lack of an identifiable cause precipitating a secondary eosinophilia, and (3) symptoms and signs of organ involvement. About 30% of patients will have either a myeloproliferative condition (chronic eosinophilic leukaemia) or hypereosinophilia mediated by clonal expansion of specific T-cells producing interleukin-5 (IL-5). Clinical features—common manifestations are (1) cardiac— endomyocardial damage typically leads to a restrictive cardio- myopathy; (2) neurological—strokes related to thromboemboli, encephalopathy, and polyneuropathy; (3) dermatological (e.g. angio-oedema, urticarial lesions); and (4) pulmonary—infiltrates of eosinophils may be seen in any part of the lung, sometimes leading to pulmonary fibrosis. Treatment—patients without organ damage do not require treat-

ment. Aside from supportive care: (1) chronic eosinophilic leukaemia— may respond to tyrosine kinase inhibitors (e.g. imatinib); and (2) nonmyeloproliferative hypereosinophilic syndrome—may respond to high-dose corticosteroids, with hydroxycarbamide, interferon-α or anti-IL-5 monoclonal antibody used in refractory cases. Introduction Eosinophilia is associated with distinct diseases that include hel- minth parasitic infections, allergic diseases, and varied diseases of often ill-defined cause. In comparison with other leucocytes, eosinophils are distin- guished by their morphologies, constituents, products, and asso- ciations with specific diseases. The cytokine interleukin-5 (IL-5), specific in promoting the development, differentiation, and release of bone marrow-derived eosinophils, is principally responsible for increases in eosinophilopoiesis. Eosinophils are normally tissue- dwelling cells primarily distributed in those tissues with an epithe- lial interface with the environment, including the gastrointestinal and lower genitourinary tracts. Eosinophils are distinguished mor- phologically from neutrophils by their cytoplasmic granules, which uniquely contain crystalloid cores visible by electron microscopy. Within these granules are four specific cationic proteins: major basic protein, eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin. The heavy content of these cationic granule proteins, which bind acidic dyes such as eosin, are respon- sible both for the identifying tinctorial properties of eosinophils and for many of the functional properties of eosinophils. Eosinophils are sources of over four dozen cytokines, and many, if not all, of these are stored preformed within eosinophil granules and cytoplasmic vesicles. In addition to their content of preformed proteins, eo- sinophils synthesize lipid mediators, including the 5-lipoxygenase pathway-derived eicosanoid, leukotriene C4. Eosinophils have roles in normal homeostatic functioning, including adipocyte biology, and in the pathogenesis of allergic diseases and in other immuno- logical responses. The potential functional roles of eosinophils in parasite–host defence, although often assumed to be helminthotoxic effector cells, are proving to be more complex and varied. Eosinophils normally number less than 450/μl in the blood with a mild diurnal variation, being slightly higher in the morning and falling as endogenous glucocorticosteroid levels rise. Blood eosino- phil numbers do not, however, always reflect the extent of eosinophil involvement in affected tissues in various diseases, and at times, as in eosinophilic pneumonias, eosinophils may be recruited into in- volved tissues without a concomitant increase in enumerable blood eosinophils. Eosinopenia, diminished blood eosinophil levels, oc- curs with corticosteroid administration and is frequent with active bacterial and viral infections. Thus, even normal blood eosinophil numbers in a febrile patient suggest that an illness is not simply due to a bacterial or viral infection. Some, but not necessarily all, patients with sustained blood eo- sinophilia can develop organ damage, especially cardiac, as found in hypereosinophilic syndromes (HES), and patients with sustained eosinophilia should be monitored for evidence of cardiac disease. Diseases associated with eosinophilia
Infectious diseases Parasitic diseases Eosinophilia is not elicited by infections with protozoan parasites (with the exceptions of the intestinal parasites Isospora belli and

 Dientamoeba fragilis), but rather characteristically by multicel- lular helminth parasites. Magnitudes of eosinophilia tend to par- allel the extent of tissue invasion, especially by helminth larvae. Eosinophilia may be absent in established infections which are well contained within tissues or are solely intraluminal within the gastrointestinal tract (e.g. ascaris, tapeworms). Even with helminth diseases, superimposed bacterial infections (e.g. in dis- seminated strongyloidiasis) can suppress expected eosinophilia. In patients with eosinophilia, geographical and dietary histories are pertinent in suggesting potential exposures to helminth para- sites. Stool examinations for diagnostic ova and larvae should be obtained, and for strongyloidiasis, in which

stool exams lack sensitivity, serological testing should be performed. In addition, for several helminth parasites that cause eosinophilia, diagnostic parasite stages are never present in faeces. Hence, negative stool specimens do not necessarily exclude a helminth aetiology for eosinophilia, and examination of appropriate blood or tissue bi- opsies and/or serological tests, as guided by clinical findings and exposure histories, may be needed to diagnose specific tissue- or blood-dwelling infections, including trichinellosis and filarial infections. Other infectious diseases The characteristic response in acute bacterial and viral infections is eosinopenia. The fungal disease, coccidioidomycosis, either following primary infection, at times with progressive dissem- inated disease, or with central nervous system infection (with cerebrospinal fluid eosinophilia), may be associated with eo- sinophilia. Cerebrospinal fluid eosinophilia may be present with cryptococcosis. Basidiobolomycosis may be associated with eosinophilia. HIV and retroviral infections Eosinophilia may be associated with HIV infections as a result of adverse reactions to medications or adrenal insufficiency in pa- tients with AIDS from cytomegalovirus and other infections. In addition, eosinophilia, often modest, is observed in some HIV- infected patients and may accompany eosinophilic folliculitis in HIV infection. Eosinophilia frequently develops with HTLV-1 infections. Allergic and immunological disorders Common allergic diseases, including allergic rhinitis, asthma, and atopic dermatitis, are accompanied by tissue eosinophil infiltration and usually modest blood eosinophilia. The occurrence of marked blood eosinophilia suggests the presence of other diseases, such as EGPA. Medication-related eosinophilias Therapeutic agents, including herbal or ‘natural’ therapies, can elicit eosinophilia. Eosinophilia may develop without other manifest- ations of adverse drug reactions, such as rashes or drug fevers. In the absence of organ involvement, blood eosinophilia by itself need not mandate cessation of drug therapy, if such is medically indi- cated. Drug-induced blood eosinophilia, however, should prompt an evaluation of whether organs, including the lungs, kidneys, and heart, are involved in the eosinophil-associated drug reaction. If organ involvement develops, cessation of drug administration is necessary. Some cytokines are potential causes of eosinophilia. Granulocyte– macrophage colony-stimulating factor (GM-CSF) and IL-2 can cause prominent blood and tissue eosinophilia and, less commonly, eosinophil-associated diseases, including eosinophilic pneumonia and eosinophilic endomyocardial fibrosis. Diverse agents, including many antimicrobial agents and nonsteroidal anti-inflammatory agents, may elicit pulmonary eosinophilia. Blood eosinophilia is usually, but not always, present; if blood eosinophilia is absent, sputum or bronchoalveolar lavage eosinophilia is necessary to help make the diagnosis. In drug-induced acute interstitial nephritis, eosinophilia is common in the involved kidneys, urine, and at times, the blood. In addition to eosinophilia, fever, rash, and arthralgia support the diag- nosis, but these are commonly absent in cases of drug-induced acute interstitial nephritis. Eosinophiluria is not uniformly present in all with drug-induced interstitial nephritis. Acute necrotizing eosinophilic myocarditis is a serious but un- common type of hypersensitivity myocarditis, with reactions to medications, responsible in some cases. A syndrome of hepa- titis with eosinophilia can be a manifestation of drug reactions. Other medication-related eosinophilic responses include drug- induced hypersensitivity vasculitis, the DRESS syndrome (drug- induced rash, eosinophilia, and systemic symptoms), and forms of gastroenterocolitis.
Immunological disorders The several genetic hyper-IgE syndromes are characterized by recurrent staphylococcal abscesses of the skin, lungs, and other sites, pruritic dermatitis, hyperimmunoglobulinaemia E, and blood, sputum, and tissue eosinophilia. Eosinophilia is charac- teristic of Omenn’s syndrome, combined immunodeficiency with hypereosinophilia, and is present in about 25% of subjects with IgG4-related disease Eosinophil infiltration accompanies rejection of lung, kidney, and liver allografts. Tissue and blood eosinophilia occur early in the re- jection

process. Myeloproliferative and neoplastic diseases The HES are considered in a later section. Eosinophilia may ac- company chronic myeloid leukaemia and the M4Eo subtype of acute myeloid leukaemia. Blood eosinophils may be elevated in the nodular sclerosing form of Hodgkin lymphoma. Some patients with carcinomas, especially of mucin-producing epi- thelial cell origins, have blood eosinophilia. Eosinophilia may accompany angio-immunoblastic lymphadenopathy, mycosis fungoides, Sézary syndrome, lymphomatoid papulosis, and sys- temic mastocytosis. Pulmonary syndromes Diverse eosinophilic pulmonary syndromes are noted in Box 22.3.8.1. Skin and subcutaneous diseases Various cutaneous diseases can be associated with a heightened level of blood eosinophils (Box 22.3.8.1). In episodic angio-oedema with eosinophilia, recurrences are marked by prominent blood

 eosinophilia, significant angio-oedema, at times with excessive weight gain due to fluid retention, and less frequently by fever. Gastrointestinal diseases Eosinophilia is common with eosinophilic gastroenteritis and eo- sinophilic oesophagitis, and tissue eosinophils are found in inflam- matory bowel diseases and collagenous colitis. Rheumatological diseases The principal eosinophil-related vasculitis is EGPA. Most of these are antineutrophil cytoplasmic antibody test negative and may be difficult to distinguish from a HES. Cutaneous necrotizing eosinophilic vasculitis with hypo complementaemia and eosinophilia, a distinct vasculitis of small dermal vessels which are extensively infiltrated with eosinophils, may occur in patients with connective tissue diseases. Eosinophilia may uncommonly accompany rheumatoid arthritis itself but is more commonly due to adverse reactions to medications or con- comitant vasculitis. Endocrine diseases Loss of normal adrenoglucocorticosteroid production causes in- creased blood eosinophilia. Other disorders The syndrome of atheromatous cholesterol embolization can be as- sociated with eosinophilia and eosinophiluria. Rare kindreds with hereditary eosinophilia have been recognized. Irritation of serosal surfaces, as in eosinophilic pleural effusions and during chronic peritoneal dialysis, can be associated with eosinophilia. Hypereosinophilic syndromes Patients with pronounced and prolonged eosinophilia not associ- ated with other clinical diseases noted previously had been classified previously as having the idiopathic HES. More recently, it has be- come clear that the HES include a clinically heterogeneous diverse group of eosinophilic disorders. For myeloproliferative and lympho- cytic variants of HES, aetiologies are now known, yet for most others with HES underlying aetiologies remain to be delineated. Definition Chusid and colleagues proposed three defining criteria for the then named idiopathic HES that may can now be modified and updated. Contemporary criteria include the following: Box 22.3.8.1 Diseases and disorders associated with eosinophilia Infectious diseases • Helminth parasites • Coccidioidomycosis • Other infections—infrequent, but includes HIV-1 and HTLV-1 Allergic and immunological disorders • Allergic rhinitis, asthma • Medication-related eosinophilias • Immunological diseases: hyperIgE syndromes, Ommen’s syndrome, and IgG4-related diseases • Transplant rejections Myeloproliferative and neoplastic disorders • Hypereosinophilic syndromes • Leukaemia, notably M4Eo subtype of acute myeloid leukaemia • Lymphoma- and tumour-associated, notably with nodular sclerosing Hodgkin lymphoma • Systemic mastocytosis Pulmonary syndromes • Parasite-induced eosinophilic lung diseases:

— Transpulmonary passage of developing larvae (Löffler syndrome): patchy migratory infiltrates, especially ascaris

— Tropical pulmonary eosinophilia: miliary lesions and fibrosis; height- ened immune responses to lymphatic filariae with increased IgE and antifilarial antibodies

— Pulmonary parenchymal invasion: paragonimiasis

— Heavy haematogenous seeding with helminths: disseminated stron- gyloidiasis, trichinellosis, schistosomiasis, larva migrans

— Allergic bronchopulmonary aspergillosis • Chronic eosinophilic pneumonia: dense often peripheral infil- trates, fever; blood eosinophilia may be absent; may be antecedent to EGPA • Acute eosinophilic pneumonia—acute presentation, often without blood eosinophilia; diagnosed by bronchoalveolar lavage or biopsy • EGPA vasculitis: small- and medium-sized arteries; perivascular eo- sinophilia early and granulomas and necrosis later; asthma often antecedent; extrapulmonary, for example, neurological, cutaneous, cardiac, or gastrointestinal vasculitic involvement likely • Drug- and toxin-induced eosinophilic lung diseases • Other: neoplasia, hypereosinophilic syndromes, bronchocentric granulomatosis Skin and subcutaneous diseases • Skin diseases—atopic dermatitis, blistering diseases, including bullous pemphigoid, urticarias, drug reactions • Diseases of pregnancy: pruritic urticarial papules and plaques syndrome, herpes gestationis • Eosinophilic pustular folliculitis • Eosinophilic cellulitis (Wells' syndrome) • Kimura's disease and angiolymphoid hyperplasia with eosinophilia • Shulman's syndrome (eosinophilic fasciitis) • Episodic angio-oedema with eosinophilia—recurrent periodic epi- sodes with fever, angio-oedema, and secondary weight gain; may be longstanding without untoward cardiac dysfunction Gastrointestinal diseases • Eosinophilic gastroenteritis—(1) blood eosinophilia; (2) eosinophil cell infiltrates in the mucosa, muscularis, or serosa; (3) oedema of stomach or intestines; and (4) absence of extraintestinal involvement • Inflammatory bowel disease and collagenous colitis—eosinophils in tissue lesions Rheumatological diseases • EGPA vasculitis • Cutaneous necrotizing eosinophilic vasculitis Endocrine disease • Hypoadrenalism: Addison's disease, adrenal haemorrhage, hypopituitarism Other causes of eosinophilia • Atheromatous cholesterol embolization • Hereditary • Serosal surface irritation, including peritoneal dialysis and pleural eosinophilia

22.3.8 Eosinophilia 5257 • Eosinophilia in excess of 1.5 × 109/litre of blood. The eosinophilia needs to be sustained over 1 month, but does not require the older prior 6-month duration, especially if therapies are needed. • Lack of an identifiable parasitic, allergic, or other aetiologies for secondary eosinophilia. As noted later (see 'Aetiologies'), some forms of HES now have identified aetiologies. Among parasitic aetiologies of eosinophilia, it is especially im- portant to exclude Strongyloides stercoralis, which may persist for decades and be difficult to diagnose solely by stool examinations, not only because of its capacity to cause marked eosinophilia mimicking HES, but also because it, unlike other helminthic causes of marked eosinophilia, can develop into a disseminated, often fatal, disease (hyperinfection syndrome) in patients given immunosuppressive corticosteroids. • Evidence by symptoms and signs of organ involvement. This older criterion has been modified to include patients with eosino- philia who do not yet exhibit evidence of organ involvement. Not all patients with prolonged eosinophilia develop organ involve- ment and many have benign courses. These patients are often not reported or subjected to evaluation at referral centres due to the absence of eosinophil-associated disease. Blood eosinophilia per se does not warrant therapy in the absence of evidence of con- comitant organ involvement. Aetiologies HES encompass a spectrum

of hypereosinophilic disorders, for which aetiologies are now recognized for a couple of HES variants: • Myeloproliferative variants—these represent forms of chronic eosinophilic leukaemia. The most common form arises from an interstitial deletion on chromosome 4q12 that leads to fusion of the FIPL1 (FIP1-like 1) and PDGFRA genes that generates a pro- tein with constitutively active receptor tyrosine kinase activity. Rearrangements of the PDGFRB and FGFR1 genes are additional causes of chronic eosinophilic leukaemia. In addition, clonal ab- normalities in the eosinophil lineage have been detected in a small number of women using X-linked polymorphisms. • Lymphocytic variants—these represent causes of HES mediated by clonal expansions of specific T-cells. The most common are due to CD3–CD4+ T-cell subsets and less frequently CD3+CD4–CD8– or other T-cell subsets. These clonal T-cells elaborate eosinophil-stimulating IL-5 and often other Th2-associated cyto- kines, including IL-4. • Other—over half of patients with HES currently have still un- defined aetiologies for their eosinophilia. Clinical features With the evolving recognition of variant forms of HES, some clinical features are more common with myeloproliferative, lymphocytic, or other variants of HES. Myeloproliferative HES is rare in women, whereas other variants of HES have no sex bias. HES tend to occur between the ages of 20 and 50 years, al- though cases have developed in children. Initial manifestations may be due to sudden cardiac or neurological complications, but tend to be more insidious and present over months or longer. Eosinophilia may be detected only incidentally. Other frequent presenting symptoms include tiredness, cough, breathlessness, muscle pains, angio-oedema, rash, sweating, pruritus, or retinal lesions. Patients with HES do not exhibit a propensity to bacterial or other infections. Haematological manifestations The defining haematological abnormality is sustained eosinophilia. Total leucocyte counts are usually less than 25 × 109/litre, with be- tween 30 and 70% eosinophils, but extremely high leucocyte counts (>90 × 109/litre) develop in some patients and are associated with a poor prognosis. Eosinophils in the blood may be mature or less commonly can include numbers of eosinophilic myeloid precursors. Eosinophils often exhibit morphological abnormalities including diminished granule numbers, cytoplasmic vacuolization, and nu- clear hypersegmentation. Some patients with HES will have an absolute neutrophilia along with their eosinophilia. Serum vitamin B12 and tryptase levels are often elevated in myeloproliferative variant HES and should be as- sayed. Anaemia is present in some patients. Bone marrow findings demonstrate increased numbers of eosinophils, often 30 to 60%, with a shift to the left in eosino- phil maturation. Increased numbers of myeloblasts are not usu- ally seen. Myelofibrosis and splenomegaly are more frequent in myeloproliferative variant HES. Cardiac manifestations In HES, the heart is a commonly affected organ due to the devel- opment of endomyocardial damage leading to a restrictive car- diomyopathy. This distinct form of cardiac involvement may also complicate other varied diseases marked by sustained eosinophilia, including eosinophilia with carcinomas or lymphomas, eosino- philia from GM-CSF or IL-2 administration or drug reactions, and less commonly eosinophilia from helminthic infections such as trichinellosis, visceral larva migrans, and filariasis. However, many patients with eosinophilia do not develop any evidence of endomyocardial damage; hence in addition to increased num- bers of eosinophils, the pathogenesis of eosinophil-mediated car- diac damage probably involves some, as yet ill-defined, activating events that promote eosinophil-mediated endomyocardial damage. Patients with sustained eosinophilia should be monitored by troponin assays and echocardiography or cardiac magnetic reson- ance imaging for evidence of cardiac disease. Cardiac damage progresses through three stages, the first involving acute necrosis in the early weeks, the second involving the development of endocardial thrombi over many months, and the final stage being the fibrotic stage after a couple of years of disease. The risks of developing cardiac disease in two series of pa- tients

with HES were not related to the extent of eosinophilia or duration of disease. Those who developed evident cardiac disease were more likely to be male and to have splenomegaly, thrombocytopenia, elevated levels of vitamin B12, hypogranular or vacuolated eosinophils, and abnormal early myeloid pre- cursors in their blood. Cardiac involvement is more common in the myeloproliferative than the lymphocytic variants of HES. Neurological manifestations Neurological complications may be of three types. The first type is due to thromboemboli originating from the left ven- tricle, which may occur before cardiac disease is demonstrable

 by echocardiography and can be the presenting manifestation of HES. The second type of neurological disease is primary central nervous system dysfunction, presenting as an encephalopathy including changes in behaviour, confusion, ataxia, and memory loss, and exhibiting upper motor neuron signs with increased muscle tone, deep tendon reflexes, and a positive Babinski sign. Impaired cognitive abilities may persist for months. The patho- logical basis for this form of diffuse central nervous system dis- ease remains unknown. Peripheral neuropathies constitute the third type of neurological dysfunction. Symmetric or asymmetric polyneuropathies manifest by sensory deficits, painful paraesthe- siae, or mixed sensory and motor deficits are most common, but mononeuritis multiplex occurs with HES (as well as with EGPA), as do radiculopathies and muscle atrophy due to denervation. Biopsies of affected nerves generally show an axonal neuropathy with varying degrees of axonal loss and no evidence of vasculitis or contiguous eosinophil infiltration. Cutaneous manifestations The skin is one of the most frequently involved organs, especially with lymphocytic variant HES. The most common skin manifest- ations are of two types: either angio-oedematous and urticarial lesions, or erythematous, pruritic papules, and nodules. Some patients with angio-oedema and eosinophilia have a syndrome of episodic angio-oedema and eosinophilia (Gleich’s syndrome) and many of these have lymphocytic variant HES. Particularly incapacitating mucocutaneous manifestations of HES are mu- cosal ulcers that may occur in the mouth, nose, pharynx, penis, oesophagus, stomach, and anus. Pulmonary manifestations Pulmonary involvement is reported in about 40% of HES pa- tients, the commonest respiratory symptom being a chronic, per- sistent, generally nonproductive cough. The basis for this may be sequestration of eosinophils in pulmonary tissues, although most symptomatic individuals have clear chest radiographs. Pulmonary involvement in HES may also be secondary to con- gestive heart failure, pulmonary emboli originating from right ventricular thrombi, or primary infiltration of the lungs by eo- sinophils. Infiltrates may be diffuse or focal without a predilection for any region of the lungs, in contrast to the often peripheral in- filtrates in chronic eosinophilic pneumonia (see Chapter 18.14.2). Pulmonary fibrosis may develop over time, especially in those with cardiac fibrosis. Other manifestations Arthralgias, large joint effusions, cold-induced Raynaud’s phe- nomenon, and digital necrosis of fingers or toes can occur with HES. Although myalgias are frequent, focal myositis or poly- myositis occur only uncommonly. Gastrointestinal tract in- volvement can accompany HES, and 20% of patients at some time may have diarrhoea. Eosinophilic gastritis, enterocolitis, or colitis may be present. Pancreatitis and sclerosing cholangitis occur rarely. Hepatic involvement with HES includes chronic active hepatitis and the Budd–Chiari syndrome from hepatic vein obstruction. Diagnosis Patients with myeloproliferative HES due to the FIP1L1-PDGFRA fusion can be identified by polymerase chain reaction or by evaluating the associated deletion of the CHIC2 gene by fluor- escence in situ hybridization. Bone marrow biopsy with cyto- genetics may identify less common myeloproliferative variants. Lymphocytic variants of HES are diagnosed based on both per- ipheral T-cell phenotyping by flow cytometry and assessments of clonal T-cell receptor rearrangements. Treatment For patients with myeloproliferative HES, therapy for chronic eo- sinophilic leukaemia is

with imatinib or related tyrosine kinase in- hibitors. For those eosinophilic patients without organ damage, no therapy need be administered. There is no clear threshold value of blood eosinophilia that predicts organ involvement or damage. For HES patients without myeloproliferative variants requiring therapy, prednisolone is the initial agent, administered at 60 mg/day in adults. For those not responsive to prednisolone or needing a steroid-sparing regimen, daily hydroxycarbamide or interferon-α (1–10 million units/day or three times a week) are options. Anti-IL-5 monoclonal antibodies may also prove to be an additional therapy for HES. Medical management of cardiac complications, including ar- rhythmias and congestive heart failure, is important and effective in the longer-term management of HES, as is surgical replacement of damaged valves. Although early reports emphasized the mor- tality due to this disorder, many of the deaths were due to con- gestive heart failure and complications of endomyocardial damage. If the sequelae of organ damage, especially to the heart, can be managed, many patients with HES can have a prolonged course. FURTHER READING Akuthota P, Weller PF (2012). Eosinophil pneumonias. Clin Microbiol Rev, 25, 649–60. Gotlib J (2017). World Health Organization-defined eosinophilic dis- orders: 2017 update on diagnosis, risk stratification, and manage- ment. Am J Hematol, 92, 1243–59. Klion AD, Weller PF (2014). Eosinophilia and eosinophil-related dis- orders. In: Adkinson NF, Jr et al. (eds) Allergy: principles and prac- tice, 8th edition, pp. 1205–23. Elsevier, London. Lefevre G, et al. (2014). The lymphoid variant of hypereosinophilic syndrome. Medicine, 93, 255–66. Ogbogu PU, et al. (2009). Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol, 124, 1319–25. Valent P, et al. (2012). Pathogenesis and classification of eosinophil disorders: a review of recent developments in the field. Expert Rev Hematol, 5, 157–76. Williams, KW, Milner JD, Freeman AF (2015). Eosinophilia associ- ated with disorders of immune deficiency or immune dysregulation. Immunol Allergy Clin N Am, 35, 523–44. Wilson ME, Weller PF (2011). Eosinophilia. In: Guerrant RL, Walker DH, Weller PF (eds) Tropical infectious diseases: princi- ples, pathogens and practice, 3rd edition. pp. 939–49. Elsevier, Philadelphia.

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