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| Clinical Utility of Molecular Testing in  the Investigation of Eosinophilia  Diagnostic utility   * Hypereosinophilia (≥1.5 x 109/L) and hypereosinophilic syndrome (HES, with evidence of organ dysfunction) have varied aetiologies including secondary (reactive), primary (clonal) and idiopathic1,2. * Eosinophilia is most commonly reactive (*e.g.* allergy, infection, autoimmune disease, medications etc*.*) and therefore reactive causes should generally be excluded prior to investigation of a haematological neoplasm. * A number of haematological neoplasms may be accompanied by an eosinophilia in which the eosinophils are part of the neoplastic clone. Additionally, eosinophilia may be reactive (non-clonal) to an underlying haematological or solid organ malignancy. * Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement is a family of diseases recognised in the WHO 5th edition3. Patients may present with myeloproliferative neoplasm, myelodysplastic/myeloproliferative neoplasm, *de novo* or secondary leukaemias or lymphomas. Eosinophilia is a common, but not invariable, feature. Specifically defined entities under this category include gene rearrangements of *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *FLT3*, and *ETV6*::*ABL1* fusion. * Rarer fusion genes reported include *ETV6*::*FGFR2*, *ETV6*::*LYN*, *ETV6*::*NTRK3*, *RANBP2*::*ALK*, *BCR*::*RET* and *FGFR1OP*::*RET*. Other rare fusion genes with potentially novel partners are possible. * In the appropriate clinicopathological context, consider testing for *JAK2*/*CALR*/*MPL* (classic MPN), *KIT* (systemic mastocytosis) or another clonal markers (chronic eosinophilic leukaemia). Both *KIT* and *FIP1L1*::*PDGFRA* may rarely coexist4. * While somatic mutation detection is one of the diagnostic criteria for chronic eosinophilic leukaemia (CEL), it is important to exclude all possible reactive causes of eosinophilia before making this diagnosis as many myeloid mutations are also observed in age-related clonal haematopoiesis3,5. * Activating *STAT5B* mutations have been reported in CEL or other myeloid neoplasms in association with eosinophilia, as well as lymphocyte-variant hypereosinophilia when occuring in T-cell population6.   Prognostic UTILITY   * Myeloid/lymphoid neoplasms with *PDGFRA* or *PDGFRB* rearrangement generally have a good prognosis with tyrosine kinase inhibitor treatment, especially when in chronic phase7,8. * The prognosis for myeloid/lymphoid neoplasms with other gene fusions is generally less favourable but also depends partly on the disease phase at presentation9.   BIOMARKERS OF RESPONSE TO THERAPY   * Myeloid/lymphoid neoplasms with *PDGFRA* or *PDGFRB* rearrangement are especially responsive to tyrosine kinase inhibitors such as imatinib8,10. * Other fusions including *FGFR1*, *ABL1*, *JAK2* and *FLT3* fusions can be variably targeted by tyrosine kinase/multi-kinase inhibitors.   References  **1.** Butt NM, et al. Guideline for the investigation and management of eosinophilia. *Br J Haematol* 2017; **176**(4): 553-72. **2.** Klion A. Hypereosinophilic syndrome: approach to treatment in the era of precision medicine. *Hematology Am Soc Hematol Educ Program* 2018; **2018**(1): 326-31. **3.** WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; forthcoming. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.fr. **4.** Schmitt-Graeff AH, et al. The FIP1L1-PDGFRA fusion gene and the KIT D816V mutation are coexisting in a small subset of myeloid/lymphoid neoplasms with eosinophilia. *Blood* 2014; **123**(4): 595-7. **5.** Jaiswal S, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014; **371**(26): 2488-98. **6.** Umrau K, et al. Activating STAT5B mutations can cause both primary hypereosinophilia and lymphocyte-variant hypereosinophilia. *Leuk Lymphoma* 2023; **64**(1): 238-41. **7.** Rohmer J, et al. Epidemiology, clinical picture and long-term outcomes of FIP1L1-PDGFRA-positive myeloid neoplasm with eosinophilia: Data from 151 patients. *Am J Hematol* 2020; **95**(11): 1314-23. **8.** Cheah CY, et al. Patients with myeloid malignancies bearing PDGFRB fusion genes achieve durable long-term remissions with imatinib. *Blood* 2014; **123**(23): 3574-7. **9.** Metzgeroth G, et al. Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions: reevaluation of the defining characteristics in a registry-based cohort. *Leukemia* 2023; **37**(9): 1860-7. **10.** Cools J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; **348**(13): 1201-14. |