Investigation of an incidental finding of eosinophilia

Hannah Sims, Wendy N Erber

The causes of eosinophilia fall into three categories (reactive disorders, clonal disorders of the bone marrow, and hypereosinophilic syndrome). This article outlines the appropriate use of investigations to establish the cause of eosinophilia.

A 57 year old man presented to his general practitioner with symptoms of a persistent dry cough and general fatigue. He had no notable medical history; he was a non-smoker and was not taking any regular medication. Clinical examination was unremarkable. A full blood count showed haemoglobin 141 g/L (normal range 130-180 g/L), mean cell volume 92 fL (80-100 fL), platelets 178×10⁹/L (150-400×10⁹/L), and leucocytes 9×10⁹/L (4-13×10⁹/L). The leucocyte differential showed neutrophils 4.3×10⁹/L (2-8×10⁹/L), lymphocytes 3×10⁹/L (1-4×10⁹/L), monocytes 0.5×10⁹/L (0.2-0.8×10⁹/L), and eosinophils 8.2×10⁹/L (0.1-0.6×10⁹/L). The blood film confirmed the presence of the eosinophilia and the eosinophil morphology appeared normal. Red cells, other leucocytes, and platelets were also morphologically normal. On the basis of the blood appearances the reporting haematologist favoured a reactive cause for the eosinophilia (such as infection, allergy, and hypersensitivity disorders; vasculitis; and autoimmune disorders). The haematologist recommended a repeat blood count to establish whether the eosinophilia was persistent, and investigations to determine the aetiology.

What is the next investigation?

Eosinophilia is a common abnormality present in 1-1.5% of blood counts in the United Kingdom (personal observation (WNE)). The causes of eosinophilia can be grouped into three categories: reactive (non-clonal or secondary) disorders; clonal (primary) disorders of the bone marrow; and hypereosinophilic syndrome.

Reactive (non-clonal or secondary) disorders

The most common disorders associated with an eosinophilia are infection (especially parasitic—schistosomiasis, hookworm, giardia, filaria, strongyloides), drugs (such as sulfonamides, penicillins, carbamazepine), allergy, and hypersensitivity disorders (such as asthma, acute urticaria, and atopic dermatitis); these account for >95% of cases. Less common reactive causes are Churg-Strauss syndrome, connective tissue and autoimmune diseases, and other infections (such as bacterial, fungal).

Clonal (primary) disorders of the bone marrow

These disorders are rare and include chronic myeloid leukaemia and chronic eosinophilic leukaemia. Eosinophilia may also be present in Hodgkin lymphoma and T cell lymphoma.

Hypereosinophilic syndrome

This is extremely rare, accounting for <1% of cases of eosinophilia.

The underlying cause of the eosinophilia may be evident from the:

- Clinical history (such as atopy, medication history)
- Extent of the eosinophilia (for example, when it is caused by atopy, the eosinophil count is rarely >2×10⁹/L, whereas an eosinophil of >10×10⁹/L is rare in reactive conditions other than parasitic infections and drug reactions). Reactive eosinophilias may be transient and resolve within 24 hours of appropriate treatment, as in acute asthma
- Eosinophil morphology: in a reactive eosinophilia the morphology is generally normal (figure) and may be accompanied by a neutrophilia. In the rare primary or clonal disorders, the eosinophils may have morphological abnormalities (such as variation in cell size and distribution and number of cytoplasmic granules). There may be accompanying red cell abnormalities (such as macrocytosis), circulating myeloid precursors, blast cells, or thrombocytosis.
A careful review of the blood film by the haematologist may therefore help in determining whether the eosinophilia is likely to be reactive or primary and guiding further investigations for the underlying aetiology.

To further establish the cause requires a more extensive history and clinical examination. Clinical history should inquire about recent foreign travel, medications (including non-prescription), rashes, and contact with animals; this should identify the more common reactive causes of eosinophilia. Clinical examination should specifically assess respiratory (such as for asthma, infection) function, cardiac function, and the skin. The box lists appropriate pathology investigations to further elucidate the cause.

If no identifiable cause for the eosinophilia has been found or if the eosinophilia (>1.5×10⁹/L) persists for three months or is rising without an obvious cause, the patient should be referred to a haematologist. Additional investigations by the haematologist will help in distinguishing between a reactive and primary clonal disorder of the bone marrow. Bone marrow aspiration and trephine biopsy will be done to assess the morphology, and this may lead to a specific diagnosis. Genetic tests may be performed on the marrow sample as specific genetic abnormalities occur in many of the malignancies (lymphoid and myeloid) associated with eosinophilia. For example, in chronic eosinophilic leukaemia there is a deletion of material on chromosome 4, resulting in a FIP1L1-PDGFRα fusion gene. These bone marrow tests may be supplemented by computed tomography for radiological evidence of a lymphoid malignancy.

The outcome
In our patient, the clinical history and primary investigations did not identify a reactive or secondary cause of the eosinophilia. The eosinophilia was persistent and rising without obvious cause so he was referred to a haematologist for further investigation. Bone marrow aspiration and trephine biopsy showed marked hyperplasia of eosinophil precursors and mature eosinophils, without an increase in blast cells. Genetic analysis identified the FIP1L1-PDGFRα fusion gene, and chronic eosinophilic leukaemia was diagnosed. He was started on imatinib, a tyrosine kinase inhibitor, with an excellent response. The blood eosinophil count and bone marrow morphology returned to normal and genetic monitoring at six months showed no evidence of the FIP1L1-PDGFRα fusion gene. He continues taking imatinib with regular blood counts and genetic monitoring under the care of the haematologist.

Chronic eosinophilic leukaemia is a rare malignancy that predominantly occurs in middle aged men and must be distinguished from the many (and more common) causes of reactive eosinophilia. Chronic eosinophilic leukaemia is a multisystem disorder characterised by a peripheral blood eosinophilia and tissue infiltration by the eosinophils. End organ damage, especially of the heart and lungs, occurs as a result of eosinophil degranulation and release of cytokines and humoral factors. The aim of treatment with imatinib is to protect the patient from long term complications associated with eosinophilia and from end organ damage, such as impaired respiratory function and cardiac failure.

Contributors: Both authors reviewed the literature and wrote the article. WNE is the guarantor.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

LESSON OF THE WEEK
When a cyst is not a cyst

J M Batchelor,¹ S E Handfield-Jones²

Atypical dermatological “cysts,” especially painful, enlarging, or unexpected ones, may be malignant and need urgent referral

We present a series of cases in which scalp lesions were diagnosed clinically as cysts, but turned out to be malignant lesions. The cases are relevant to anyone diagnosing or treating skin lesions, as well as to those involved in allocating funding for treatment.

Case reports

Case 1
A 75 year old man presented to his general practitioner with a lump on his scalp. His medical history included aplastic anaemia but he was otherwise well. The GP examined the lump and diagnosed a loculated epidermoid cyst. During excision he found that it adhered to the underlying tissues and so removed it piecemeal. Histological examination of the specimen was difficult because the sample was fragmented, but the lesion was clearly malignant. Plastic surgeons performed a wide excision, and histology showed a tumour with features of a poorly differentiated sebaceous carcinoma.

The differential diagnosis included a metastatic tumour, so extensive investigations were carried out to identify a primary malignancy, but none was found. The patient continued under close follow-up and showed no sign of recurrence 12 months after initial surgery.

Case 2
An 11 year old girl presented to her GP with a three month history of a lump on the back of her head, which was painful and growing larger. The GP made a clinical diagnosis of an epidermoid cyst and referred her non-urgently to the general surgeons. The lesion was thought to be benign, but excision was planned because it was painful, increasing in size, or otherwise atypical (multiloculated, for example).

Histological examination showed a rare tumour known as a giant cell fibroblastoma with myxoid dermatofibrosarcomatous areas; it was widely excised, using Mohs’ micrographic surgery. This cleared the lesion completely and histological examination gave a final diagnosis of dermatofibrosarcoma protruberans. The patient remained well on review one year later.

Case 3
A 76 year old woman, who was being followed up in the dermatology clinic after excision of a malignant melanoma, mentioned a lesion in her scalp that she had had for about six years. It had enlarged recently. Her medical history was complex: she had undergone excision of multiple masses from her scalp at age 28, but she was uncertain what they were and her medical records had no details. She had been diagnosed as having “bone cancer” in her toe at age 40 (again, no records were available) and uterine carcinoma at age 46, managed by hysterectomy.

Examination of the scalp lesion showed a mobile lesion within the skin, not adherent to the underlying tissues. During surgery it became apparent that the lesion was a solid mass rather than a cyst and so it was biopsied.

Histological examination showed a poorly differentiated carcinoma with a high mitotic rate. The tumour was thought to be either a primary skin adnexal tumour or a secondary deposit from a breast, gynaecological, salivary gland, or bladder primary tumour. Full body computed tomography showed multiple lung metastases. A mammogram and full ear, nose, and throat examination and nasendoscopy were unremarkable.

Palliative radiotherapy led to considerable shrinkage of the tumour. The patient also received eight cycles of capecitabine chemotherapy, which was tolerated well. Computed tomography a year later showed complete resolution of the lung metastases, and she remained well two and a half years later.

Discussion

“Cystic” lesions on the scalp may in fact be malignant, and anyone examining such a lesion should think twice before diagnosing a “benign cyst.” Many lumps on the scalp do turn out to be benign cysts, but they may be more serious, particularly in children (in whom cysts are less common), in elderly patients who have not previously had cysts, or if the lesion is painful, increasing in size, or otherwise atypical (multiloculated, for example).

Scalp cysts are most common in young adults¹ and in older patients in whom cysts have presented previously, but a previous diagnosis of a benign cyst does not preclude the possibility of a subsequent malignant lesion. In our cases, the correct diagnosis resulted from thorough investigation, and eventually the patients received appropriate treatment that led to a satisfactory clinical outcome. This would not have been the case if the lesions had simply been diagnosed as benign cysts.

The diagnoses in our cases are rare, and these patients were seen over a period of several years. Even so, malignant lesions should always be considered as a differential diagnosis when assessing a cyst on the scalp. Sebaceous carcinomas, such as in case 1, most commonly develop on the head and neck. Dermatofibrosarcoma protruberans, such as in case 2, most commonly presents on the trunk and limbs, but in up to 15% of cases occurs on the head and neck.² Cutaneous metastases from breast, gastric,
The risks of radiation exposure related to diagnostic imaging and how to minimise them

In the box of sources and selection criteria in this Clinical Review by HE Davies and colleagues (BMJ 2011;342:d947, print publication 12 March, pp 589-93) we referred to the Royal College of Radiologists as the Royal College of Radiology.

The management of abdominal aortic aneurysms

A mix-up while spelling out a mathematical symbol during editing led to an error in the section “How are AAAs managed?” of this clinical review by David Metcalfe and colleagues (BMJ 2011;342, print publication 19 March, pp 644-9). In the opening paragraph we should have said: “Patients with aneurysms less than 5.5 cm [not “greater than 5.5 cm”] should be entered into an ultrasound surveillance programme.” The author wants to clarify for readers that 5.5 cm is the threshold for surgical intervention and that it would not be safe to routinely manage these patients with surveillance alone.

Strengthening the reporting of genetic risk prediction studies: the GRIPS statement

At the end of this Research Methods and Reporting article by A Cecile J W Janssens and colleagues (BMJ 2011;342:d631, print publication 19 March, pp 640-3), we mistakenly omitted PLoS Medicine from the list of journals that are also publishing the article.

Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis

The authors of this research paper, Keith Hawton and colleagues (BMJ 2009;338:b2270, print publication 22 August 2009, pp 435-8), have advised us that the data used in their study have since been revised by the Office for National Statistics because of problems identified in the coding of deaths involving analgesic compounds.