Clinicopathological Case Conference of Haematological Medicine

Episodes 8:

Acid-Loving Cell and the Potentials

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Index Case 1

- 22 years
- Male
- Seen in AE
- Sudden onset SOB in the morning
- Associated Chest pain
- 6 weeks history of

non specific joint pain

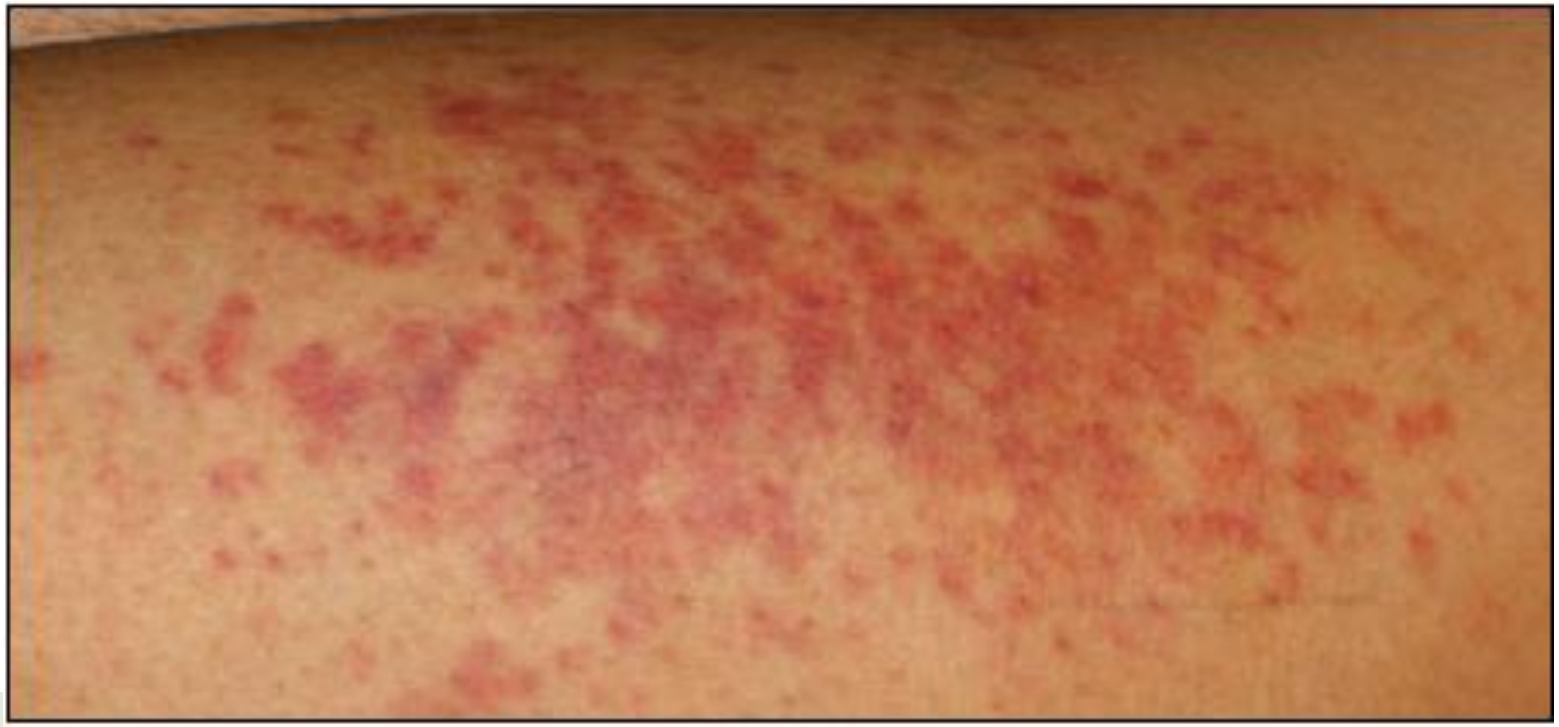
Generalised skin rash

- NO PMH, never been in Hospital
- Return home from Manchester University
- NO Drugs history
- NO recent foreign travel
- NO FH of note

AE evaluation

- Hypoxic , Sats 78% Ambient air (High flow oxygen started)
- Pulse 120 SR,
- Temperature 37.7 C
- BP 90/55
- ECG sinus tachy
- BM 5
- Urine dips: trace of protein and few WCC
- MSU sent

- Respiratory: wheezes and bilateral fine crackles
- CVS: Sinus Tachy, No other abnormal sounds
- GI: Mild generalised abdominal tenderness
- SKIN:



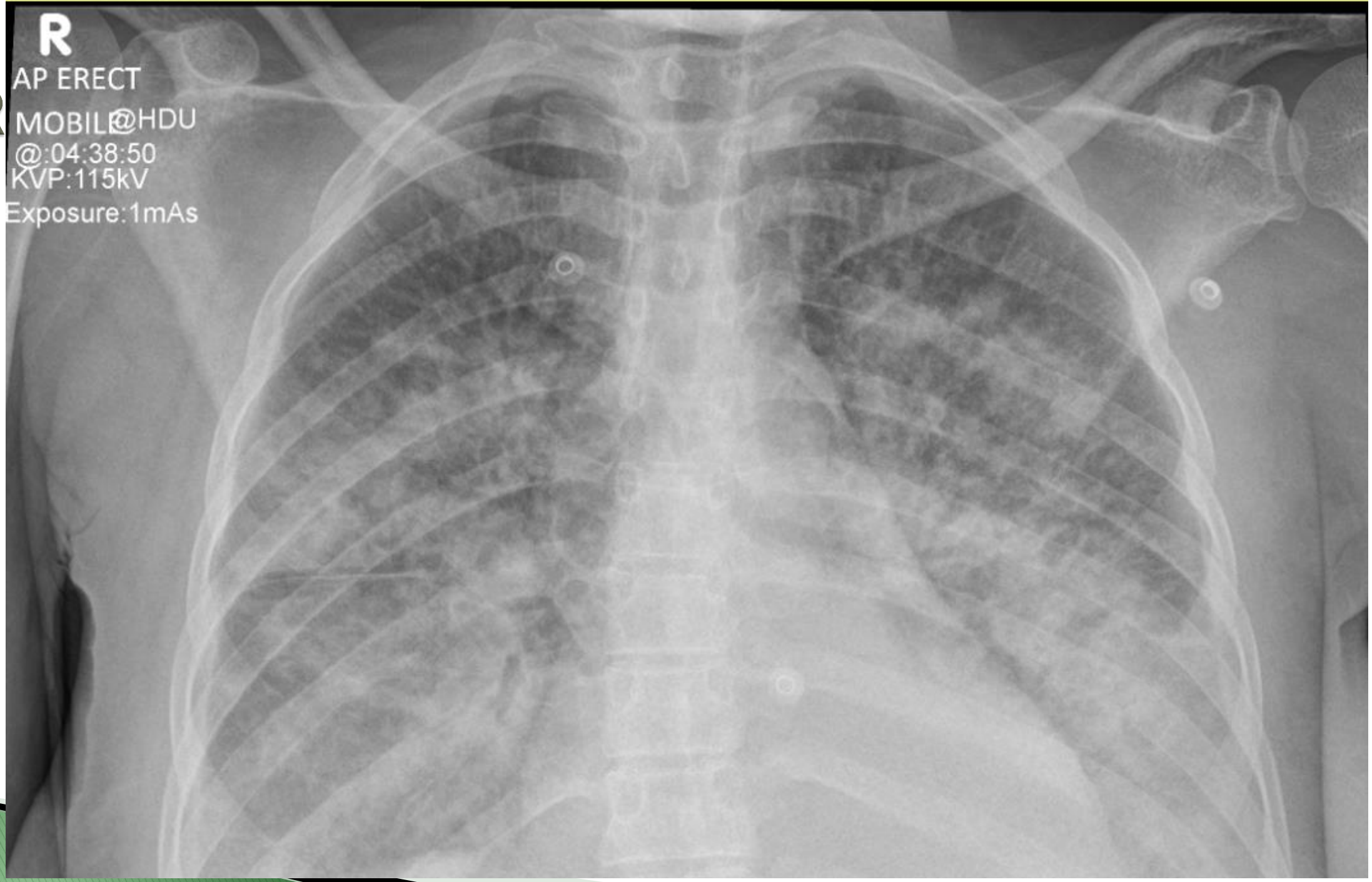
- Joints and locomotors: NAD
- CNS: Grossly intact

- Bloods sent
- CXR -Done
- Blood culture sent
- Respiratory viral PCR sent
- Admitted under medics

Bloods

BONE PROFILE					
	Albumin	*	24	g/L	35 - 50
	Alkaline phosphatase		52	U/L	30 - 130
	Calcium		1.96	mmol/L	
	Adjusted calcium		2.32	mmol/L	2.2 - 2.6
C REACTIVE PROTEIN					
	C reactive protein	*	26	mg/L	<5
FULL BLOOD COUNT					
	HAEMOGLOBIN	*	102	g/L	115 - 165
	WHITE CELL COUNT	*	13.0	10^9/L	4.0 - 11.0
	PLATELET COUNT		264	10^9/L	150 - 400
	HCT	*	0.32	L/L	0.37 - 0.46
	RCC		4.15	10^{12}/L	3.8 - 5.8
	RDW	*	16.9	%	11.0 - 14.8
	MCV	*	76.9	fL	80 - 100
	MCH	*	24.6	pg	27.0 - 32.0
	Differential Count				
	Neutrophil Count		7.11	10^9/L	1.7 - 7.5
	Lymphocyte Count	*	0.49	10^9/L	1.0 - 4.5
	Monocyte Count		0.31	10^9/L	0.2 - 0.8
	Eosinophils	*	5.07	10^9/L	0.0 - 0.4
	Basophils		0.01	10^9/L	0.0 - 0.1
	Differential comment		Results telephoned.		
LIVER FUNCTION TEST					
	Liver Function Test				
	Total protein	*	55	g/L	60 - 80
	Globulin		31	g/L	20 - 35
	Total bilirubin		6	umol/L	0 - 21
	ALT		23	U/L	<35
MAGNESIUM					
	Magnesium		0.83	mmol/L	0.7 - 1.0
PHOSPHATE					
	Phosphate	*	1.62	mmol/L	0.8 - 1.5
UREA & ELECTROLYTES					
	Sodium		135	mmol/L	133 - 146
	Potassium		4.2	mmol/L	3.5 - 5.3
	Urea		4.1	mmol/L	2.5 - 7.8
	Creatinine		59	umol/L	45 - 95
RHEUMATOID FACTOR					
	Rheumatoid factor		<10	U/mL	0 - 14

CXR



What are the differentials

- what next steps would you like to take

Differentials suggested

- Allergic reactions
- Adult onset Asthma
- Pulmonary oedema
- Atypical infections
- Connective tissue disease/Autoimmune disease
- Systemic vasculities
- Hypereosinophilc syndromes

Would like to start Steroids early?

Or

- Would you wait to complete other specialised test first
- Would you Start steroid early and promptly arrange secondary tests

Specialised test requested

- CT
- PET CT
- CTD serology/ DsDNA/ ENA/cryoglobulins
- Virology
- Atypical infection screen
- Complement
- IgS
- Tryptase
- Lupus, cardiolipin
- Trop T
- ECHO

- CT 1 called Haematology SPR for advise
- DW Consultant haematologist
- Advised DO Bone marrow as urgent for HES
- Molecular test from BM liquid
- Start high dose steroid without delay

Bloods next day

	Bicarbonate		25	mmol/L	22 - 29
BONE PROFILE					
	Albumin	*	19	g/L	35 - 50
	Alkaline phosphatase	*	229	U/L	30 - 130
	Calcium		1.87	mmol/L	
	Adjusted calcium		2.33	mmol/L	2.2 - 2.6
C REACTIVE PROTEIN					
	C reactive protein	*	164	mg/L	<5
FULL BLOOD COUNT					
	HAEMOGLOBIN	*	89	g/L	115 - 165
	WHITE CELL COUNT	*	17.7	10^9/L	4.0 - 11.0
	PLATELET COUNT	*	596	10^9/L	150 - 400
	HCT	*	0.27	L/L	0.37 - 0.46
	RCC	*	3.68	10^{12}/L	3.8 - 5.8
	RDW	*	19.0	%	11.0 - 14.8
	MCV	*	73.4	fL	80 - 100
	MCH	*	24.3	pg	27.0 - 32.0
	Differential Count				
	Neutrophil Count	*	16.44	10^9/L	1.7 - 7.5
	Lymphocyte Count	*	0.50	10^9/L	1.0 - 4.5
	Monocyte Count	*	0.18	10^9/L	0.2 - 0.8
	Eosinophils		0.28	10^9/L	0.0 - 0.4
	Basophils	*	0.30	10^9/L	0.0 - 0.1
FULL CLOTTING SCREEN					
	Routine Coagulation				
	PT	*	15.3	seconds	10.3 - 13.3
	INR		1.2	INR	0.8 - 1.2
	Derived Fibrinogen	*	5.52	g/L	2.00 - 5.30
	APTT	*	39.9	seconds	25.7 - 35.3
	APTT Ratio	*	1.31	1/1	0.8 - 1.2
PLASMA GLUCOSE					
	Plasma Glucose		8.6	mmol/L	<11.1
LIVER FUNCTION TEST					
	Liver Function Test				
	Total protein	*	51	g/L	60 - 80
	Globulin		32	g/L	20 - 35
	Total bilirubin		10	umol/L	0 - 21
	ALT	*	78	U/L	<35

Bone marrow done the same day

BONE MARROW ASPIRATE

Bone Marrow Aspirate Report		
Indication		

Eosinophilia; and mental confusion, pulmonory infiltrates;

Quality of sample		Very Good
Bone Marrow collection site		PIC
Cellularity		Mildly increased
Megakaryocytes		Increased - normal morphology.
Erythroid		Normal
Myeloid		

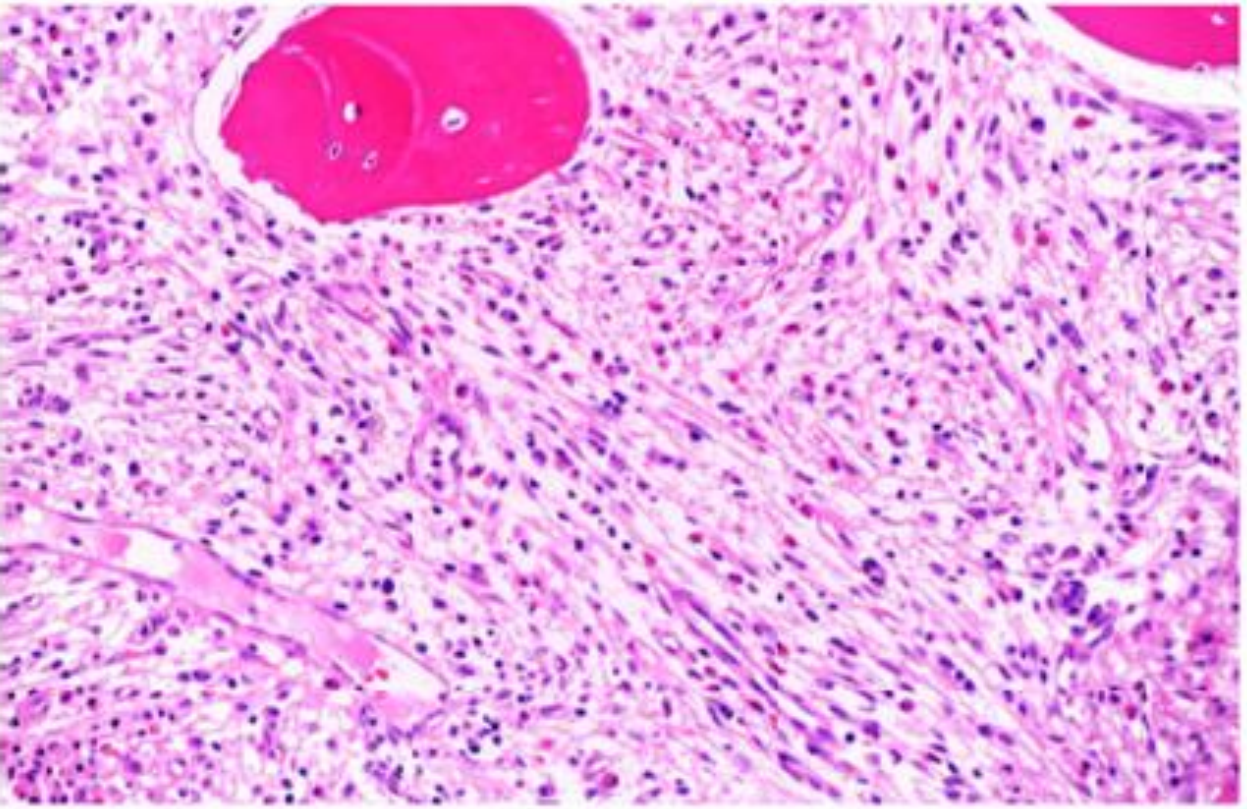
Mildly increasedd with reactive features. Eosinophils and precursors accocunt for 15% of myeloid series.

Lymphoid		Normal
Monocytes		Normal
Bone Marrow differential		
Blasts		None
Plasma cells		5% - within normal limits
Other abnormal cells		No erythrophagocytes seen.
Bone Marrow iron status		
Iron stain		ND
Bone Marrow Conclusion		
Diagnostic comment		

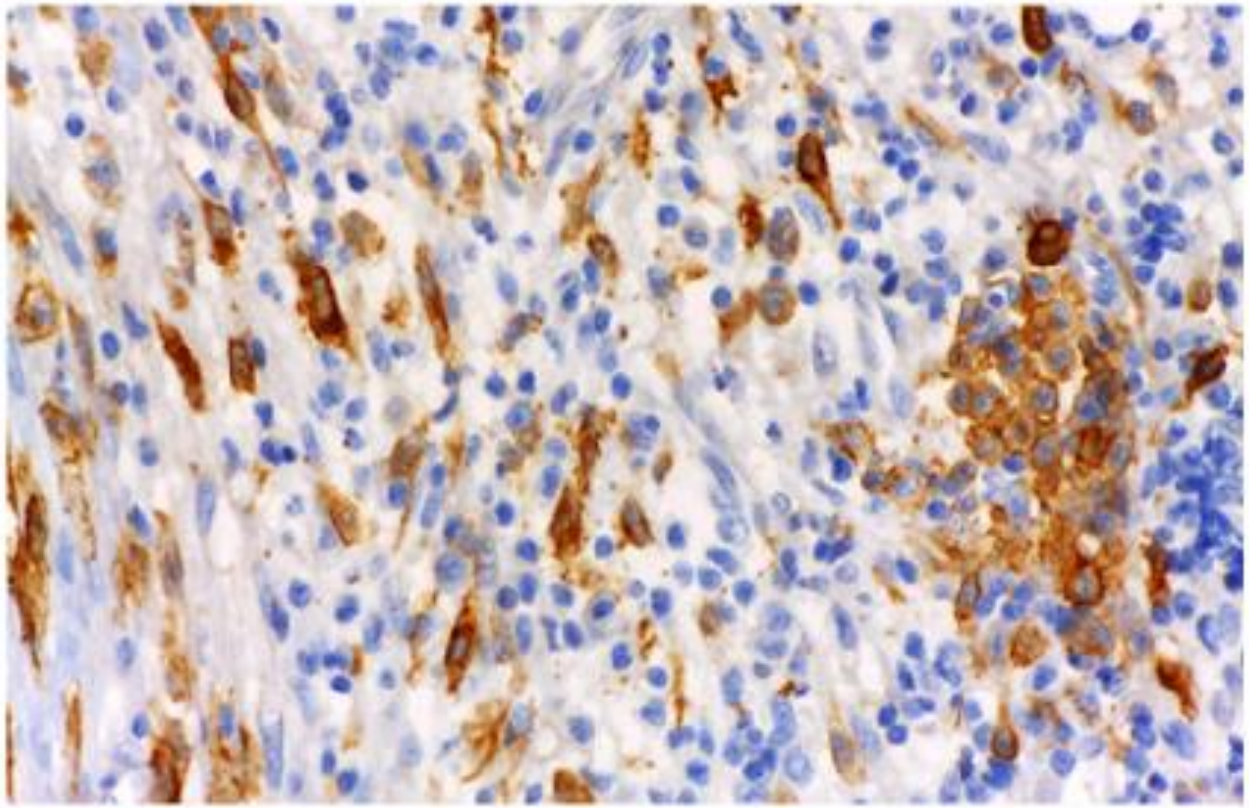
Reactive bone marrow aspirate showing 15% eosinophils - consistent with peripheral blood eosinophilia. There is no evidence of lymphoma or soslid tumour in this sample. Trephine, flow cytometry and molecular studies to follow. Overall this is a reactive aspirate with no specific diagnostic features.

Bone marrow trephine

E *FIP1L1-PDGFRA*$^{+}$ myeloid neoplasm



F *FIP1L1-PDGFRA*$^{+}$ myeloid neoplasm



Urgent molecular study requested form Bone marrow liquids

- *Results next day*

Karyotype 46 XY

Interphase FISH analysis showed evidence of

FIP1L1-PDGFRA (4q12), PDGFRB (5q32)

T and B cell Clonality study: NAD

Diagnosis

- Myeloid neoplasm with eosinophilia

Associated with

Fusion gene mutation FIP1L1-PDGFRA (4q12), PDGFRB (5q32)

- Rare entity
- Timely diagnosis and intervention is life saving

OF NOTES

- Other test including
- PET CT : CT component mild effusion and reticular shadowing bilaterally
- Serum B12 >1500
- Serum tryptase : slightly raised 12nm/ml
- ECHO: mild pericardial effusion, good LVEF 60%
- CT abdo: mild thickening of small bowel wall

treatment

- STARTED IMATINIB 100 MG (*A TYROSINE KINASE INHIBITOR*)

- CURATIVE CONDITON
- Very sensitive to Imatinib

A case 16th July 2019 not so Lucky

- 42 years old
- Joint pain and fever , unwell, confusion

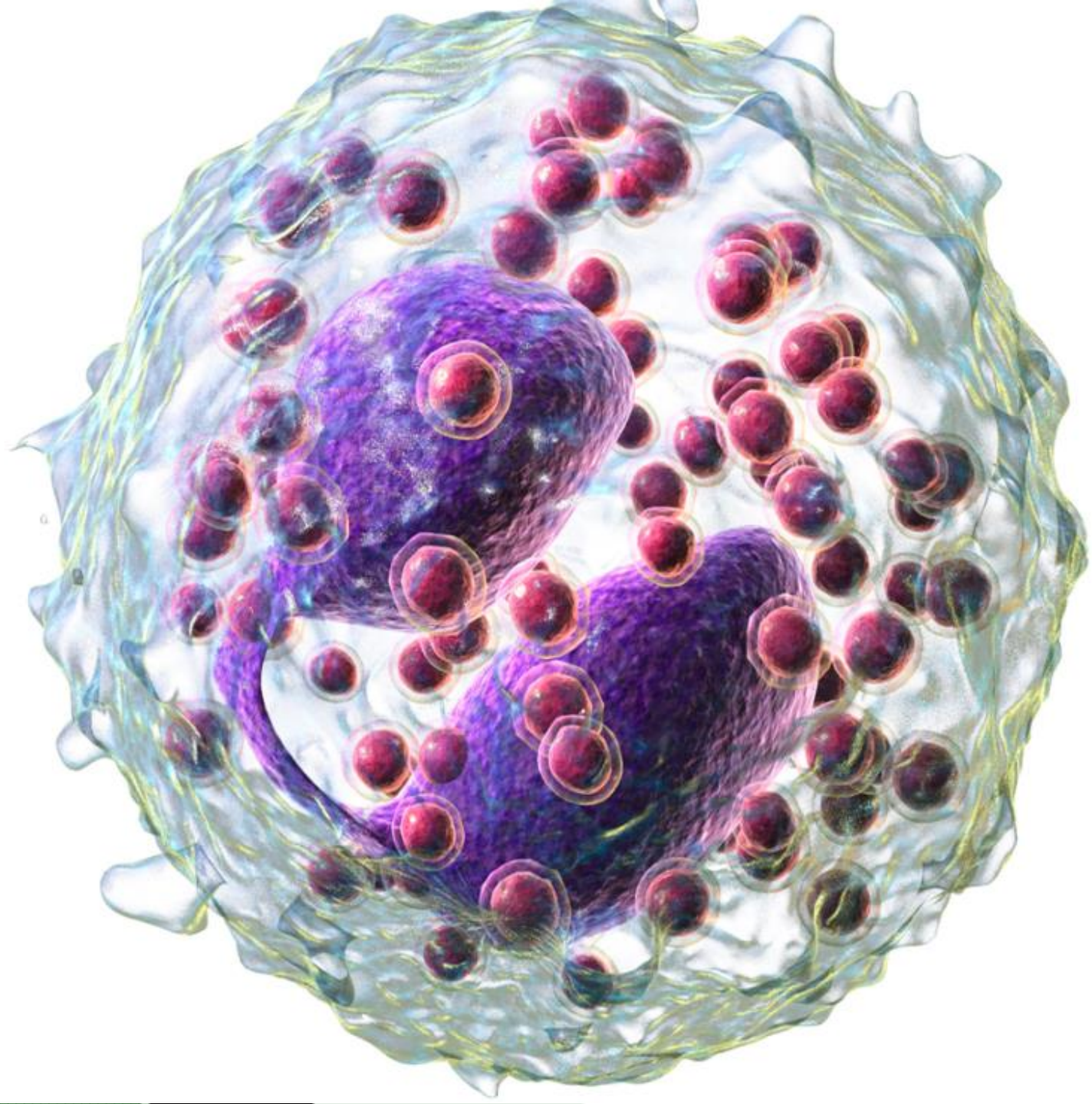
Evaluation revealed

- HB104, WCC 15 , PLT 450, Eosinophils 3.4, CRP 34
- Deteriorated rapidly
- ITU , ventilated MOF
- CT , PET, axillary nodes
- ? Vasculitis
- ?CTD
- ?Infection

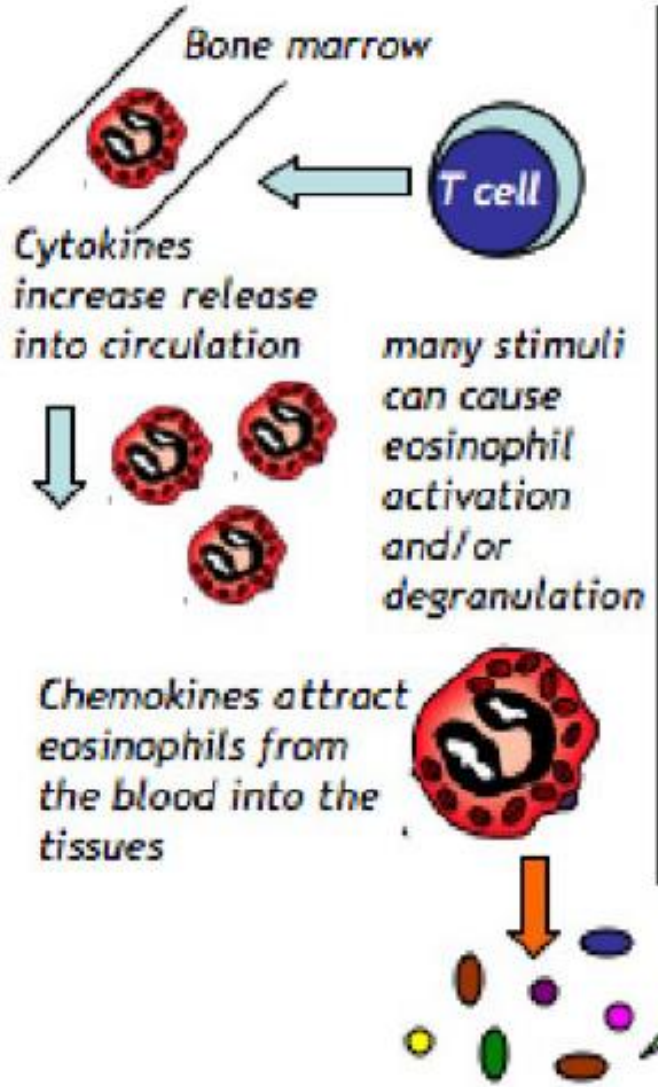
- BM molecular test: NAD
- Left axillary nodes: Reactive
- Considered ECMO-

- RIP

- Case referred to Coroner
- ? Diagnosis



eosinophilia
1.5 X 109/L (1500/mm3)



Cell-Surface Expressed Molecules

Receptors: FceRIII, CCR3, CRTH2, CD88, H4R
Adhesion molecules: CD11b, CD11c, CD62L
Others: Siglec-8

Key molecules released by eosinophils

Granule Contents:
Toxic proteins: MBP, ECP, EDN, EPO
Enzymes: lysozyme
Cytokines: GM-CSF, IL-2, IL-4, IL-5, IL-6, TNF-a
Chemokines: CCL5

Additional Secreted Products:
Lipid mediators: Leukotrienes, prostaglandins
Chemokines
Cytokines
Reactive oxygen species: NO, O2-, H2O2, OH-

Category	Examples (noninclusive)
Allergic disorders*	Asthma, atopic dermatitis
Drug hypersensitivity	Varied
Infection	
Helminth	Varied, including strongyloidiasis, hookworm infection, filariasis
Ectoparasite	Scabies, myiasis
Protozoan	Isosporiasis, *Sarcocystis* myositis
Bacterial	Chronic tuberculosis, resolving scarlet fever
Fungal	Varied, including coccidiomycosis, allergic bronchopulmonary aspergillosis
Viral	HIV
Neoplasm	Leukemia, lymphoma, solid organ adenocarcinoma
Autoimmune and idiopathic disorders†	Connective tissue disorders, sarcoidosis, inflammatory bowel disease, autoimmune lymphoproliferative disorder
Other	Hypoadrenalism, radiation exposure, cholesterol embolization, IL-2 therapy

HES indicates hypereosinophilic syndrome.

*Allergic disorders, including asthma and atopic dermatitis, are common in patients with lymphocytic variant HES (L-HES) and idiopathic HES. Consequently, the distinction between allergic disease with marked eosinophilia and HES with concomitant allergic disease may be impossible.

†Marked peripheral blood eosinophilia can occur in the setting of a wide variety of autoimmune and idiopathic disorders, particularly those characterized by abnormal lymphocyte proliferation or activation. Signs and symptoms of HES are infrequent and can be difficult to distinguish from manifestations of the underlying disorder.

General approach to treatment

The first question to address with respect to treatment of HES is whether the patient requires urgent intervention (Figure 1).

Patients presenting with potentially life-threatening complications, including cardiac, respiratory or neurologic involvement, and marked eosinophilia should be treated empirically with high-dose corticosteroids (eg, intravenous methylprednisolone at a dose of 1 mg/kg per day) to prevent progression of end organ damage.

- Although every effort should be made to obtain necessary diagnostic studies, including blood work, imaging studies, and biopsies of affected tissues before initiating corticosteroid therapy, treatment should not be delayed in the face of worsening signs and symptoms.

- In patients with aggressive disease unresponsive to several days of high-dose corticosteroids, addition of a second agent should be guided by the clinical presentation.

- Imatinib therapy should be

considered early in a male patient presenting with new onset myocarditis, respiratory and neurological symptoms and marked eosinophilia;

- whereas a female patient with a history of asthma and nasal polyps presenting with myocarditis and dramatic eosinophilia would be more likely to have Churg-Strauss vasculitis and to benefit from sustained corticosteroid therapy.

Vincristine, rapidly lower eosinophil counts in patients with HES, should be reserved for patients with rapidly progressive, life-threatening disease unresponsive to high-dose steroids and imatinib therapy.

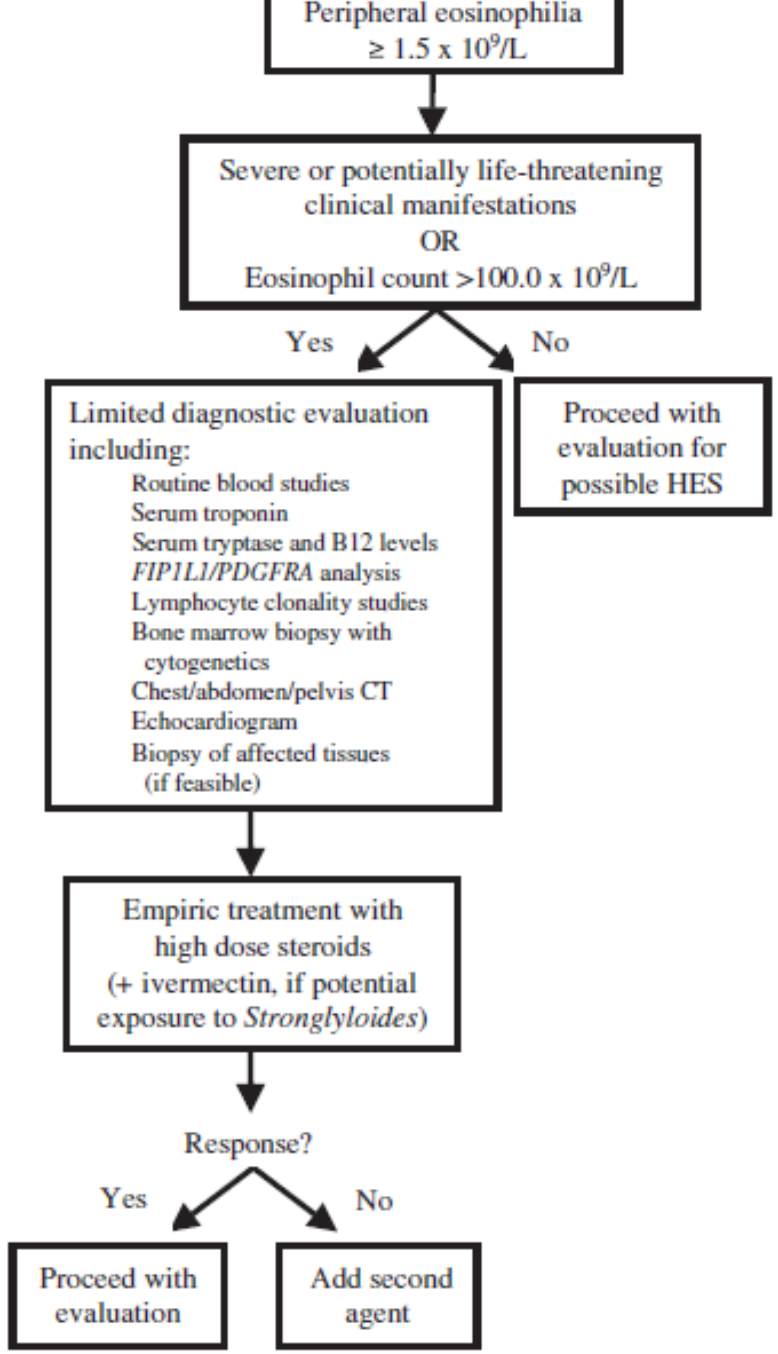
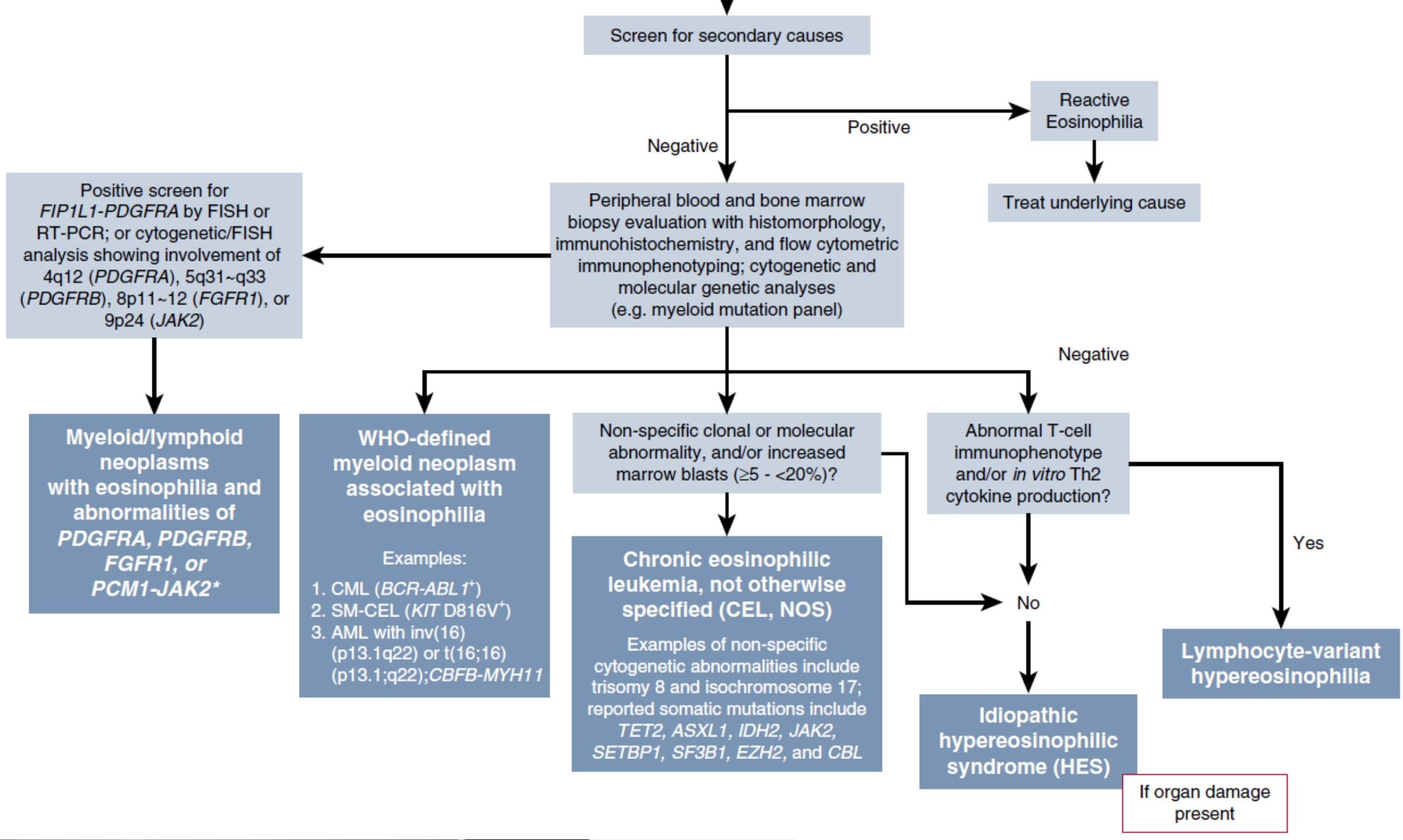


Figure 1. Initial approach to the patient with possible HES.


Screen for secondary causes
Positive
Reactive Eosinophilia
Treat underlying cause
Negative
Peripheral blood and bone marrow biopsy evaluation with histomorphology, immunohistochemistry, and flow cytometric immunophenotyping; cytogenetic and molecular genetic analyses (e.g. myeloid mutation panel)
Positive screen for FIP1L1-PDGFRA by FISH or RT-PCR; or cytogenetic/FISH analysis showing involvement of 4q12 (PDGFRA), 5q31~q33 (PDGFRB), 8p11~12 (FGFR1), or 9p24 (JAK2)
Myeloid/lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2*
Negative
WHO-defined myeloid neoplasm associated with eosinophilia
Examples:
1. CML (BCR-ABL1+)
2. SM-CEL (KIT D816V+)
3. AML with inv(16) (p13.1q22) or t(16;16) (p13.1;q22);CBFB-MYH11
Non-specific clonal or molecular abnormality, and/or increased marrow blasts (≥5 - <20%)?
Chronic eosinophilic leukemia, not otherwise specified (CEL, NOS)
Examples of non-specific cytogenetic abnormalities include trisomy 8 and isochromosome 17; reported somatic mutations include TET2, ASXL1, IDH2, JAK2, SETBP1, SF3B1, EZH2, and CBL
Abnormal T-cell immunophenotype and/or in vitro Th2 cytokine production?
Yes
Lymphocyte-variant hypereosinophilia
No
Idiopathic hypereosinophilic syndrome (HES)
If organ damage present

A good read

Guideline | Free Access |

Guideline for the investigation and management of eosinophil

Nauman M. Butt, Jonathan Lambert, Sahra Ali, Philip A. Beer, Nicholas C. P. Cross, Andrew Duncom
Joanne Ewing, Claire N. Harrison, Steven Knapper, Donal McLornan ... See all authors

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Thank you for your attention

Questions