# Consult. Confirm. CONTROL:

## with NovoSeven® (Recombinant Factor VIIa) in acquired haemophilia (AH)[1]

***Henry, 78 years old,*** *presented with severe and extensive skin bruising and blood in the stool. Henry had no prior history of bleeding.*

This advertisement is intended for Healthcare Professionals

## Your primary treatment objective in AH is to STOP THE BLEED*

**NovoSeven® is one of the first-line treatment options in AH based on:†[2,3]**

• Rapid bleed control with consistently high efficacy[4-11] • Established tolerability profile[1,4,12-15] • Simple, rapid reconstitution and administration‡ and convenient storage[1]

*Published guidelines also recommend eradicating the inhibitor with immunosuppressive therapy.
†Other first-line haemostatic treatments are also recommended.
‡NovoSeven® vial-to-vial reconstitution 2–5 mins to infuse.

**Prescribing Information NovoSeven®** Eptacog alfa (activated); recombinant Factor VIIa (rFVIIa) **Please refer to Summary of Product Characteristics for full information. Presentation:** Powder (vial) and solvent (pre-filled syringe) for solution for injection. Available in packs containing 1, 2, 5 or 8 mg rFVIIa (8 mg only available in the UK). **Uses:** Treatment of bleeding episodes and prevention of bleeding during surgery or invasive procedures in patients with:- congenital haemophilia with inhibitors to coagulation FVIII or FIX > 5 BU or who are expected to have a high anamnestic response to FVIII or FIX; - acquired haemophilia; - congenital FVII deficiency; - Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available. **Dosage:** The rFVIIa is dissolved in the accompanying solvent before use. After reconstitution the solution contains 1 mg rFVIIa/ml. Administer by intravenous bolus injection over 2-5 minutes; must not be mixed with infusion solutions or given in a drip. NovoSeven® should be administered as early as possible after the start of a bleeding episode. *Haemophilia A or B with inhibitors or expected to have high anamnestic response* Initial dose of 90 µg/kg body weight. Duration of, and interval between, repeat injections dependent on severity of haemorrhage or procedure/surgery performed. Paediatric population: Clinical experience does not warrant a general differentiation in dosing between children and adults. Children have faster clearance than adults and higher doses may be needed to obtain similar plasma concentrations as in adults. For mild to moderate bleeding episodes (including home therapy): Two dosing regimens can be recommended: i) Two to three injections of 90 µg/kg body weight administered initially at 3-hour intervals. If further treatment is required, one additional dose of 90 µg/kg can be administered. ii) One single injection of 270 µg/kg body weight. Duration of home therapy should not exceed 24 hours. Only after consultation with the haemophilia treatment centre can continued home treatment be considered. For serious bleeding episodes, initial dose 90 µg/kg body weight; dose every two hours until clinical improvement. If continued therapy indicated, dosage interval can be increased successively. Major bleeding episode may be treated for 2-3 weeks or longer if clinically warranted. For invasive procedures/surgery administer initial dose of 90 µg/kg body weight immediately before the procedure. Repeat dose at 2-3 hour intervals for first 24-48 hours. In major surgery continue dosing at 2-4 hour intervals for 6-7 days. Dosage interval may then be increased to 6-8 hours for further 2 weeks. Treatment may be up to 2-3 weeks until healing has occurred. *Acquired haemophilia* Initial dose of 90 µg/kg body weight. Further injections may be given if required. Initial dose interval should be 2-3 hours. Once haemostasis achieved, the dose interval can be increased successively *Factor VII deficiency* For bleeding episodes and for invasive procedures/surgery, in adults and children, administer 15-30 µg/kg body weight every 4-6 hours until haemostasis achieved. Adapt dose and frequency to individual. Limited clinical experience in long term prophylaxis has been gathered in paediatrics below 12 years of age, with severe clinical phenotype. *Glanzmann's thrombasthenia* For bleeding episodes and for invasive procedures/surgery administer 90 µg/kg body weight (range 80-120 µg) every 2 hours (1.5-2.5 hours). At least three doses should be administered to secure effective haemostasis. For patients who are not refractory platelets are first line treatment. In all conditions the dose schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred. **Contra-indications:** Known hypersensitivity to active substance, excipients, or to mouse, hamster or bovine protein may be a contraindication to the use of NovoSeven®. **Precautions:** Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. For severe bleeds NovoSeven® should only be administered in hospitals specialised in the treatment of patients with coagulation factor FVIII or FIX inhibitors or in close collaboration with a physician specialised in treatment of haemophilia. No clinical experience with administration of single dose of 270 µg/kg body weight in elderly patients. Home therapy should not exceed 24 hours. Possibility of thrombogenesis or induction of DIC in conditions in which tissue factor could be expected in circulating blood, e.g. advanced atherosclerotic disease, crush injury, septicaemia, or DIC. Since NovoSeven® may contain trace amounts of mouse, bovine and hamster proteins there is a remote possibility of the development of hypersensitivity. Monitor FVII deficient patients for prothrombin time and FVII coagulant activity; suspect antibody formation if FVIIa activity fails to reach expected level or bleeding not controlled with recommended doses. Thrombosis in FVII deficient patients receiving NovoSeven® during surgery has been reported but risk is unknown. Avoid simultaneous use of prothrombin complex concentrates, activated or not. Based on a non-clinical study it is not recommended to combine rFVIIa and rFXIII. **Interactions: (Irish requirement only)** Risk of a potential interaction between NovoSeven® and coagulation factor concentrates is unknown. Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided. Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and rFVIIa treatment is however limited. **Fertility, pregnancy and lactation:** Only administer to pregnant women if clearly needed. Not known if excreted in human milk; a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with NovoSeven® should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoSeven® therapy to the woman. Data from non-clinical studies as well as post-marketing data show no indication that rFVIIa has a harmful effect on male or female fertility. **Side Effects:** The frequencies of both serious and non-serious adverse drug reactions are: Uncommon (≥ 1/1,000, < 1/100): venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia); rash (including allergic dermatitis and rash erythematous); pruritus and urticaria; therapeutic response decreased - it is important that the dosage regimen of NovoSeven® is compliant with the recommended dosage; pyrexia. Rare (≥1/10,000, <1/1,000): disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT; coagulopathy; hypersensitivity; headache; arterial thromboembolic events (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia); angina pectoris; nausea; injection site reaction including injection site pain; increased fibrin degradation products; increase in alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known. Not known: anaphylactic reaction; intracardiac thrombus, flushing; angioedema. *Inhibitory antibody formation:* Post-marketing there have been no reports of inhibitory antibodies against NovoSeven® or FVII in patients with haemophilia A or B. Development of inhibitory antibodies to NovoSeven® has been reported in post-marketing observational registry of congenital FVII deficient patients. Patients with FVII deficiency, formation of antibodies against NovoSeven® and FVII is the only adverse drug reaction reported (frequency: common (≥ 1/100 to < 1/10)). Risk factors may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived FVII, severe mutation of FVII gene, and overdose of NovoSeven®. Patients with FVII deficiency treated with NovoSeven® should be monitored for FVII antibodies. *Thromboembolic events:* When NovoSeven® is administered outside approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (5.6% in patients treated with NovoSeven® versus 3.0% in placebo-treated patients) has been shown in trials conducted outside current approved indications. Safety and efficacy of NovoSeven® have not been established outside approved indications; NovoSeven® should not be used in these cases. Thromboembolic events may lead to cardiac arrest. *Patients with acquired haemophilia:* Clinical trials showed certain adverse drug reactions were more frequent (1% based on treatment episodes): arterial thromboembolic events (cerebral artery occlusion, cerebrovascular accident), venous thromboembolic events (pulmonary embolism and deep vein thrombosis), angina pectoris, nausea, pyrexia, erythematous rash and investigation of increased levels of fibrin degradation products. The Summary of Product Characteristics should be consulted for a full list of side effects. **Marketing Authorisation numbers:** NovoSeven® 1 mg (50 KIU) EU/1/96/006/008 NovoSeven® 2 mg (100 KIU) EU/1/96/006/009 NovoSeven® 5 mg (250 KIU) EU/1/96/006/010 NovoSeven® 8 mg (400 KIU) EU/1/96/006/011 (UK only) **Legal Category:** POM **(UK ONLY)- Basic NHS Price:** NovoSeven® 1 mg £525.20 NovoSeven® 2 mg £1,050.40 NovoSeven® 5 mg £2,626.00 NovoSeven® 8 mg £4,201.60 For complete prescribing information, please refer to The Summary of Product Characteristics which is available: **For Ireland from** - www.medicines.ie or by email from info@novonordisk.ie or from Medical Department, Novo Nordisk Limited, 1st Floor, Block A, The Crescent Building, Northwood Business Park, Santry, Dublin 9, Ireland; Tel: 1 850 665 665 **For UK from** – www.medicines.org.uk or from Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA; Tel: 01293 613555 or Fax: 01293 613535

**Ireland only**

Adverse events should be reported. Information about adverse event reporting is available at www.hpra.ie Adverse events should be reported to the Novo Nordisk Medical department; Tel: 1 850 665 665.

**UK only**

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 600 5055). Calls may be monitored for training purposes.

**References: 1.** NovoSeven® Summary of Product Characteristics. **2.** Huth-Kuhne A, et al. Haematologica 2009;94(4):566–575. **3.** Collins P, et al. BMC Res Notes 2010;3:161.**4.** Baudo F, et al. Blood 2012; 120(1):39–46. **5.** Borel-Derlon A, et al. Presented at the World Federation of Hemophilia (WFH) World Congress, July 24–28 2016, Orlando FL USA: Online poster PO-W-4. **6.** Bysted BV, et al. Haemophilia 2007;13(5):527–532. **7.** Fernández-Bello I, et al. Haemophilia 2017;23(1):868–876. **8.** Amano K, et al. Haemophilia 2017;23(1):50-58 **9.** Hay CR, et al. Thromb Haemost 1997;78(6):1463-1467. **10.** Sumner MJ, et al. Haemophilia 2007;13(5):451–461. **11.** Lentz SR, et al. J Blood Med 2014;5:1–3. **12.** Hedner U. Blood Rev 2015;29(S1):S4–S8. **13.** Tiede A, Worster A. Ann Hematol 2018;97(10): 1889–1901. **14.** Neufeld EJ, et al. Haemophilia 2018;24(4):e275-e277. **15.** Abshire T, Kenet G. Haemophilia 2008;14(5):898–902.



Date of preparation: November 2019 UK19NS00111

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bjh review

# Review of the clinical and pathological panopaly of systemic mastocytosis

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## Summary

Mastocytosis is a rare disease with varied presentation, myriad symptomatology and variable prognosis. Most patients present with cutaneous disease and mediator-related symptomatology with a small subset having systemic disease (systemic mastocytosis, SM). A subset of the latter develops synchronous or metachronous haematologic neoplasms (SM-AHN), most commonly chronic myelomonocytic leukaemia (CMML). Advanced systemic mastocytosis (ASM) is seen in a relatively small number of patients and is usually associated with organ dysfunction, and may present with hepatosplenomegaly, lymphadenopathy and ascites with progression to leukaemic transformation (mast cell leukaemia/acute myeloid leukaemia) occurring in a few patients. This paper discusses the clinical and pathologic features of the entire spectrum of SM in adults.

**Keywords:** mast cells, systemic mastocytosis, myeloproliferative neoplasm.

## Background

Systemic mastocytosis (SM) is a haematological neoplasm with complex diagnostic (Table I) and clinical (Table II) classifications that provide an indication of prognosis and guide treatment (Valent et al., 2001; Swerdlow et al., 2017; Valent et al., 2007; Valent et al., 2017). The spectrum of SM encompasses a heterogeneous population of patients with indolent to aggressive disease and a variable degree of symptom burden ( Scherber & Borate 2018) (Fig1). The majority of adult patients (>80%) present with mastocytosis in the skin (MIS), most commonly, maculopapular cutaneous mastocytosis (MPCM), requiring further evaluation to determine if the patient has systemic disease. Utilising the WHO criteria (Valent et al., 2001; Arber et al., 2016; Valent et al., 2017), patients with a baseline tryptase of >20 μg/l (Schwarz & Irani, 2000) and clinical findings (mediator-related symptoms, musculoskeletal symptoms, constitutional symptoms, organ dysfunction or organomegaly) proceed to biopsy of an extra-cutaneous organ. The bone marrow (BM) biopsy is standard in all patients with a suspected diagnosis of SM. A biopsy of additional organs, such as the liver, gastrointestinal tract, lymph node or body cavity fluid is recommended in those few patients where it is unclear whether the patient has local organ damage and may therefore have a diagnosis of advanced SM. A small minority of patients, who present with severe or life-threatening anaphylaxis following a bee or wasp (Hymenoptera venom) sting or idiopathic anaphylaxis, may also warrant investigation to exclude SM; this subset of patients may have lower baseline tryptase levels (<20 μg/l) and no evidence of cutaneous manifestations (Gulen et al., 2014; Zanotti et al., 2015).

At Guys and St Thomas's Hospitals Foundation Trust, we established a UK centre of excellence in mastocytosis in 2006, in association with the European Competence Network of Mastocytosis (ECNM). We have reviewed more than 500 patients in the mastocytosis service with approximately 200 patients being seen directly within the haematology service. In this review, we will discuss real patient cases to illustrate clinical and histopathological variations in the diagnosis and management of this uncommon disease. Please note patient cases used here span a decade and some pre-2016 terminology for cutaneous mastocytosis will have been applied at the time of diagnosis for some patients.

Given the variable symptomology, specific tests that are used to identify and manage SM in our routine practice include the evaluation of serum tryptase, liver function tests (LFT), renal function tests (RFT), vitamin D and calcium levels, BM examination (aspirate and trephine), biopsies from other organ systems, molecular analysis (*KIT*, extended myeloid gene panel analysis) and dual-energy X-ray absorptiometry (DEXA) scans. Whole body imaging using MRI or CT scans in patients with SM are useful to assess organomegaly and the presence of lymphadenopathy. In the context of biopsy evaluation, it is pivotal to have access to a facility

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doi: 10.1111/bjh.16288

**Table I.** Diagnostic criteria for SM (adapted from Swerdlow et al., 2017).

| |
|---|
| Diagnosis requires: |
| One major criterion + at least one minor criterion |
| Or |
| At least three minor criteria |
| Major criterion |
| Multifocal dense infiltrates of mast cells (≥15 mast cells in an aggregate) in bone marrow and/or extracutaneous organs |
| Minor criterion |
| >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology, or >25% of all mast cells in bone marrow aspirate smears are immature or atypical |
| Detection of activating point mutation at codon 816 of *KIT* in the bone marrow, blood or another extracutaneous organ |
| Mast cells in bone marrow, blood or another extracutaneous organ express CD25, with or without CD2 |
| Serum total tryptase is persistently >20 ng/ml, unless there is an associated myeloid neoplasm |

where appropriate immunohistochemistry can be performed to detect clonal mast cells.

## The normal and neoplastic mast cell

Normal mast cells are round, mononuclear cells, with abundant cytoplasm, which contain metachromatic granules in their cytoplasm (Fig 2A). In histological sections, they appear as round cells with abundant pink granulated cytoplasm and small round nuclei (Fig 2B). In healthy patients, a small number of normal mast cells are identified within the BM in a peri-sinusoidal (Fig 2B) or peri-trabecular distribution. They express mast cell tryptase (MCT) and CD117.

Neoplastic mast cells may demonstrate a range of morphologies, from the typical spindle-shaped mast cell with hypogranular cytoplasm (Fig 2C, 2), to those resembling metachromatic blasts. Less frequently, such as in **Case A**, the typical spindle-shaped neoplastic mast cell may show hypergranulation. Bi- or multilobated nuclei and/or blast-like features have been associated with a poorer prognosis (Sperr et al., 2001). Immunophenotypically, in addition to MCT and CD117, neoplastic mast cells co-express CD25 (almost 100%) and CD2 (~60%), although the sensitivity and specificity of assessing CD25 expression alone is comparable to the use of CD2 and CD25 (Jordan et al., 2001; Pardanani et al., 2004; Morgado et al., 2012). In addition, using immunohistochemical staining (rather than flow cytometry), CD25 staining is stronger and easier to assess in our experience. CD2 expression on mast cells is more frequently seen when using flow cytometry. Expression of CD30 and/or CD123 may help in identifying patients who may progress in the future, but data on this association is not particularly robust (Sotlar *et al*., 2011; Valent *et al*., 2011; Moonim *et al*., 2012; Morgado *et al*., 2013; Doyle *et al*., 2014; Blatt *et al*., 2015; Pardanani *et al*., 2016).

## Indolent systemic mastocytosis (ISM)

### *Case A*

A 45-year-old gentleman presented to dermatology with a seven-year history of rashes and facial flushing. He had no history of gastrointestinal symptoms, allergies or anaphylaxis. Clinically, the rash was in keeping with urticaria pigmentosa (now referred to as MPCM) and a skin biopsy confirmed the presence of a dermal mast cell infiltrate (Fig 3A). His tryptase level at diagnosis was raised (136 μg/l) with a normal full blood count (Table III). His BM aspirate showed 9% spindle-shaped mast cells. A BM biopsy showed 20% mast cells, which were unusually heavily granulated for mast cells (Fig 3C) and a diagnosis of ISM was made. He was managed with Fexofenadine 180 mg as required and Alendronate for his osteoporosis, and has remained stable during his seven-year follow up with no evidence of disease progression.

### *Case B (Table IV results summary)*

A 44-year-old male patient was referred with a history of four anaphylactic reactions over a period of five weeks. No triggers were identified on review by an Immunologist. He had been diagnosed with UP (now referred to as MPCM) nine years previously and received PUVA treatment. He had mild pruritus and proven allergies to latex, watermelon and shellfish. He suffered from loose bowel motions five to six times a day. No organomegaly was identified. A diagnostic BM aspirate carried out in 2009 showed 4–5% mast cells. The BM biopsy confirmed a diagnosis of SM (disease bulk 5–10%) (Fig 3). Molecular analysis [(allele-specific-polymerase chain reaction (AS-PCR)] did not identify the presence of a *KIT* mutation. He was diagnosed with ISM and treatment was started with sodium cromoglycate 200 mg TDS (three times a day), hydroxyzine hydrochloride 25 mg OD (once daily) and Adcal D3 for his osteoporosis. He carried an Epipen® in view of his current presentation. Primary Care Trust (PCT) funding allowed treatment with Imatinib 400 mg OD, which he has remained on for 10 years because of his severe anaphylaxis,. No further anaphylactic episodes occurred and he has since stopped his antihistamine and sodium cromoglycate. His tryptase level reduced from 31·1 to 11 μg/l after a year of treatment with Imatinib (Novartis pharmaceuticals).

*The pathology of indolent systemic mastocytosis.* The diagnosis, in most cases, is made on a BM biopsy. Careful examination of the aspirate often highlights scattered atypical mast cells; but in practicality this can be a time-consuming exercise. A discordance between mast cell burden on BM aspirate and trephine is well-recognised, with the mast cell burden being higher on the BM trephine—the mast cell disease burden is defined by the BM trephine. Diagnosis is made in accordance with the World Health Organisation

**Table II.** Diagnostic criteria for the variants of SM. Adapted from Swerdlow et al, 2017.

| |
|---|
| Indolent systemic mastocytosis (ISM) |
| Meets the general criteria for systemic mastocytosis (Table IIb) |
| No C findings (see below) |
| No evidence of an associated haematological neoplasm |
| Low mast cell burden |
| Skin lesions invariably present |
| Smouldering systemic mastocytosis |
| Meets the general criteria for SM (Table IIb) |
| ≥2 B findings; no C findings (see below) |
| No evidence of an associated haematological neoplasm |
| High mast cell burden |
| Does not meet the criteria for mast cell leukaemia |
| Systemic mastocytosis with an associated haematological neoplasm (SM-AHN) |
| Meets the general criteria for SM (Table IIb) |
| Meets the criteria for an associated haematological neoplasm |
| Aggressive SM |
| Meets the general criteria for SM (Table IIb) |
| ≥1 C finding (see below) |
| Does not meet the criteria for mast cell leukaemia |
| Skin lesions usually absent |
| Mast cell leukaemia |
| Meets the general criteria for SM (Table IIb) |
| Bone marrow biopsy shows diffuse infiltration by atypical, immature mast cells |
| Bone marrow aspirate smears show ≥20% mast cells |
| Leukaemic (classic) mast cell leukaemia: mast cells account for ≥10% of the peripheral white blood cell count |
| Aleukaemic variant: mast cells account for <10% of the peripheral white blood cell count |
| B findings |
| High mast cell burden (on bone marrow trephine biopsy): >30% infiltration of cellularity by mast cells and serum tryptase >200 ng/ml |
| Signs of dysplasia or myeloproliferation in non-mast cell lineage(s), but criteria are not met for definitive diagnosis of an associated haematological neoplasm, with normal or only slightly abnormal blood counts |
| Hepatomegaly without impairment of liver function, palpable splenomegaly without hypersplenism and/or lymphadenopathy on palpation or imaging |
| C findings |
| Bone marrow dysfunction caused by neoplastic mast cell infiltration ≥1 cytopenia (neutrophils count $<1.0 \times 10^9$/l, Hb < 100 g/l, platelet count $<100 \times 10^9$/l) |
| Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension |
| Skeletal involvement, large osteolytic lesions ± pathological fractures |
| Palpable splenomegaly with hypersplenism |
| Malabsorption with weight loss due to gastrointestinal mast cell infiltrates |

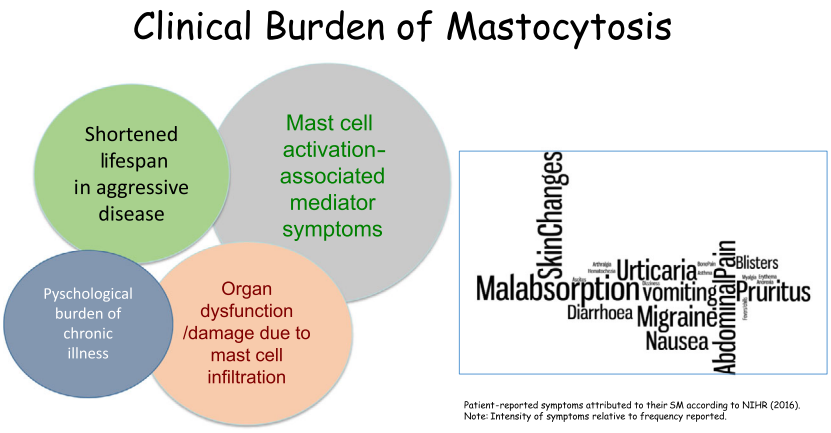


**Fig 1.** Patient-reported symptoms attributed to their systemic mastocytosis according to NIHR (2016). Note: Intensity of symptoms relative to frequency reported.

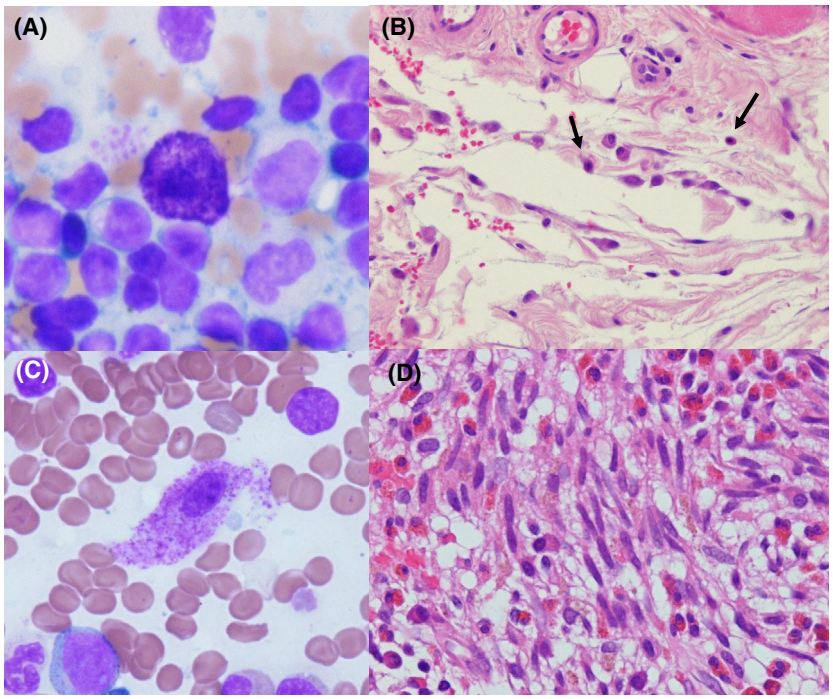


**Fig 2.** Normal and neoplastic mast cells. (A) Metachromatic granules (Giemsa 40×). (B) Perivascular mast cells (arrows) (H&E 10×). (C) Neoplastic mast cell (bone marrow aspirate (Giemsa 100×). (D) Spindle-shaped neoplastic mast cells (H&E 20×).

(WHO) major and minor criteria (Swerdlow et al., 2017) (Table I). The major criterion requires the identification of aggregates of at least 15 mast cells; these aggregates may be distributed as interstitial nodules, as paratrabecular or perivascular aggregates, or may be singly dispersed within the interstitium. In some cases, all patterns may be seen, whereas others may only show interstitial nodules. The distribution within the marrow does not correlate with disease severity. The most frequent cell morphology seen is that of spindle-shaped mast cells, surrounded by a rim of lymphocytes and eosinophils (Figs 3B and 4). Immunophenotypically, CD117 is co-expressed with either CD25 and/or CD2 (Fig 3D, 3 and 3). Well-differentiated systemic mastocytosis (WDSM) should be considered if the mast cells are predominantly round and hypergranulated and show low/negative CD25 expression, as well as lacking *KIT* D816V (Akin, 2004; Alvarez-Twose et al., 2016). These are often responsive to imatinib therapy (Alvarez-Twose et al., 2012).

*Practice points: ISM.* Allele-specific nested PCR should be used to detect *KIT* D816V in preference to next generation sequencing (NGS), owing to higher sensitivity (sensitivity of allele-specific PCR [between 1–0·01%]; digital droplet PCR [0·005%]).

If a *KIT* D816 mutation is not identified, *KIT* gene sequencing should be considered to assess for any other *KIT* mutation present (exon 17 (D815K, D816F, D816H, D816Y, D820G, E839K), exon 11 (V560G) and exon 10 (K509I, F522C, V530I, A533D).

Screening for FIP1L1-PDGFRA should be considered if eosinophilia is present.

Anaphylaxis may occur even if BM disease bulk is low.

In the absence of a *KIT* D816V mutation (<10%), Imatinib should be considered as a therapeutic option in symptomatic patients and may lead to complete response in up to 40% patients (Valent et al., 2014; Alvarez-Twose et al., 2016). Patients with mutations in the extracellular/transmembrane domain of *KIT* respond better to imatinib than patients with wild type *KIT*.

## Smouldering systemic mastocytosis (SSM)

*Case C (Table V results summary)*

A 42-year-old male patient was referred to haematology via dermatology in 2010. He was diagnosed with cutaneous mastocytosis at the age of 16 years. He was minimally symptomatic with intermittent pruritus not requiring any medication. In 2008, he sought a dermatology opinion as his rash had significantly worsened, covering most of his body and causing cosmetic concerns, as well as daily pruritus, despite regular loratadine. Dermatology assessment confirmed telangiectasia macularis eruptiva perstans (TMEP) on skin biopsy. He was treated with an attenuated course of PUVA, which was stopped as he did not gain any significant benefit. He had no gastrointestinal symptoms , allergies and had never had any anaphylactic reactions. A diagnostic BM

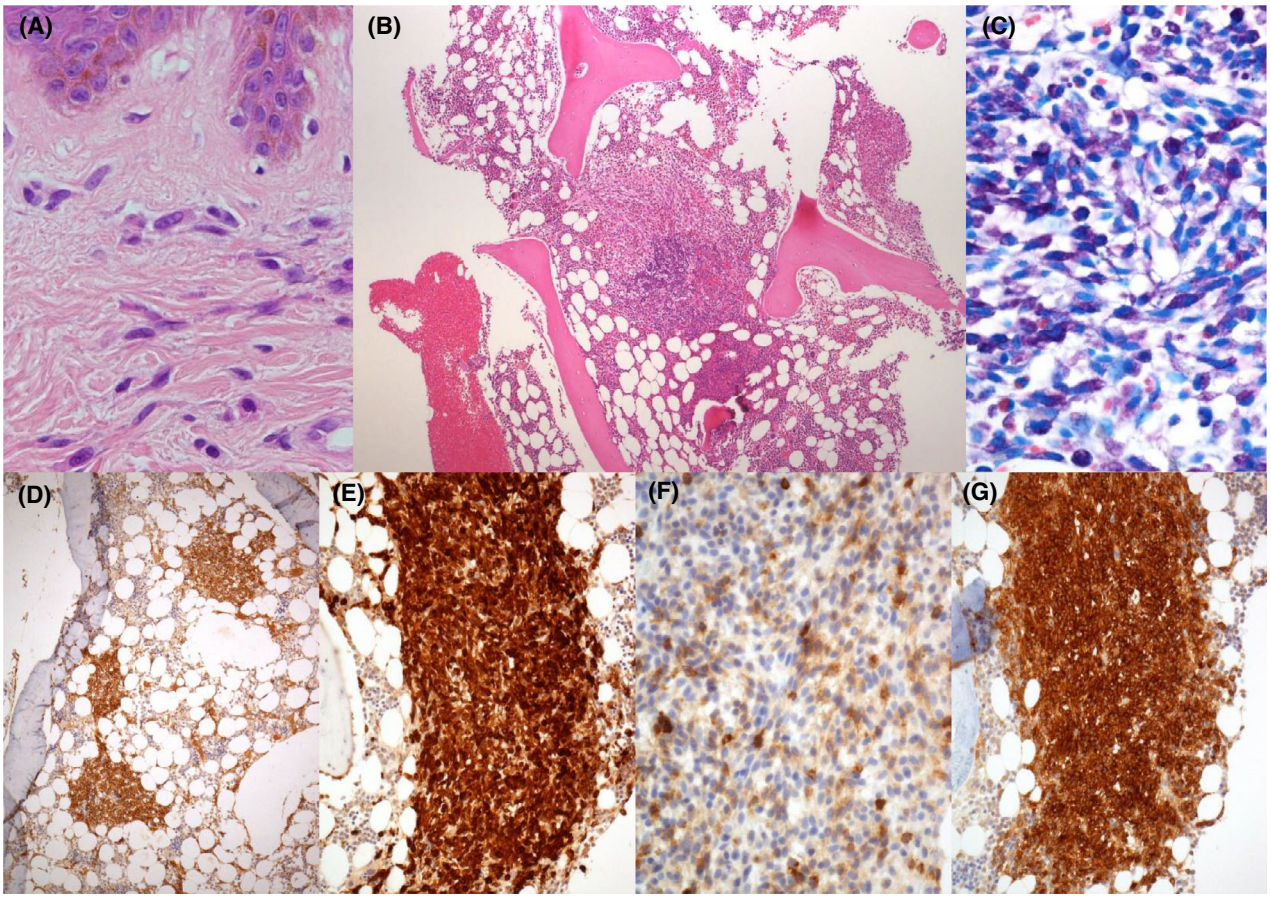


**Fig 3.** Indolent systemic mastocytosis (Case A). (A) Skin showing dermal spindle-shaped mast cells (H&E 40×). (B) Diagnostic nodular lesion of mastocytosis in bone marrow (H&E 2×). (C) Granulated spindle-shaped neoplastic mast cells (Giemsa 40×). (D) Mast cell tryptase. (E) CD117. (F) CD2. (G) CD25.

**Table III.** Results of investigations and clinical findings taken at diagnosis.

| | |
|---|---|
| Full blood count | |
| Haemoglobin, g/l | 146 |
| WCC, $\times 10^9$/l | 7·1 |
| Neutrophil count, $\times 10^9$/l | 4·8 |
| Eosinophil, $\times 10^9$/l | 0·1 |
| Platelets, $\times 10^9$/l | 225 |
| Liver and bone profile | |
| Bilirubin μmol/l | 9 |
| ALT IU/L | 28 |
| ALP IU/L | 55 |
| Albumin g/l | 50 |
| Corr. Ca mmol/l | 2·36 |
| Specialist tests | |
| BMT disease bulk | 20% |
| Serum tryptase (μg/l) | 136 |
| *KIT* | D816V positive |
| Clinical features | |
| Splenomegaly | None |
| Hepatomegaly | None |
| DEXA scan | Osteoporosis |

**Table IV.** Results of investigations and clinical findings taken at diagnosis.

| | |
|---|---|
| Full blood count | |
| Haemoglobin, g/l | 155 |
| WCC, $\times 10^9$/l | 8·7 |
| Neutrophil count, $\times 10^9$/l | 5·7 |
| Eosinophil, $\times 10^9$/l | 0·3 |
| Platelets, $\times 10^9$/l | 485 |
| Liver and bone profile | |
| Bilirubin μmol/l | 3 |
| ALT IU/l | 45 |
| ALP IU/l | 76 |
| Albumin g/l | 52 |
| Corr. Ca mmol/l | 2·38 |
| Specialist tests | |
| BMT disease bulk | 5–10% |
| Serum tryptase (μg/l) | 31·2 |
| *KIT* | Negative |
| Clinical features | |
| Splenomegaly | None |
| Hepatomegaly | None |
| DEXA scan | Osteoporosis |

**Table V.** Results of investigations and clinical findings taken at diagnosis.

| | |
|---|---|
| Full blood count | |
| Haemoglobin, g/l | 14·6 |
| WCC, $\times 10^9$/l | 14·6 |
| Neutrophil count, $\times 10^9$/l | 10·5 |
| Eosinophil, $\times 10^9$/l | 1·0 |
| Platelets, $\times 10^9$/l | 221 |
| Liver and bone profile | |
| Bilirubin μmol/l | 6 |
| ALT IU/l | 29 |
| ALP IU/l | *266* |
| Albumin g/l | 51 |
| Corr. Ca mmol/l | 2·38 |
| Specialist tests | |
| BMT disease bulk | 30% |
| Serum tryptase (μg/l) | 427 |
| *KIT* | D816V positive |
| Clinical features | |
| Splenomegaly | Splenic tip palpable 2 cm below costal margin |
| DEXA scan | Normal |

biopsy was carried out in March 2011 and he was started on fexofenadine 180 mg OD. He was monitored and had two acute admissions for anaphylaxis following a single dose of aspirin (2014) and gastroduodenal bleeds (2015), requiring blood product support and endoscopic laser treatment. These complications of his SM were treated and he is on regular anti-H1 and anti-H2 blockade. Re-evaluation of his disease status in 2015 and 2016 showed an increase in BM disease bulk over time, with accompanying increase in organomegaly evaluated by a CT Scan with increasing abdominal lymphadenopathy and a rising alkaline phosphatase, which peaked at 540 IU/l. Midostaurin was commenced on a compassionate use programme in November 2016 on which he remains well, asymptomatic and with clinical resolution of his organomegaly and TMEP rash.

*Pathology.* The initial bone marrow transplant (BMT) from March 2011 (Fig 5A–E) shows 30% involvement by SM, in the form of areas of paratrabecular fibrosis, within which are infiltrates of epithelioid and spindle-shaped mast cells, as well as a dispersed interstitial infiltrate. The mast cells show aberrant expression of CD2 and CD25. The subsequent BM biopsy from July 2016 (Fig 5F, G) shows a slight increase in SM disease bulk to approximately 40%. The mast cells show aberrant expression of CD25, CD2 and CD123, but not CD30. A retroperitoneal lymph node biopsy (Fig 5H–J) performed in July 2016 showed expansion of interfollicular areas by pale, plump, round-to-oval mast cells aberrantly expressing CD25 with heterogeneous expression of CD2, but no expression of CD123 or CD30. A subsequent BM biopsy in October 2016 (Fig 5K–M) showed 50% involvement by SM, in the form of sheets and nodules of round and spindle mast cells expressing CD25 and CD2. The mast cells show focal expression of CD30 and focal expression of CD123.

NB: All his aspirates had <20% mast cells at each biopsy.

This is a typical case of SSM, with high mast cell disease burden (BM disease bulk >30% and serum tryptase >200 ng/ml), splenomegaly and lymphadenopathy.

It has been shown that higher frequency of multilineage involvement of *KIT* D816V in patients with ISM is an independent factor for progression and this may be the aetiology for progression from ISM or SSM for a small number of patients (Escribano et al., 2009).

### *Case D*

A 67-year-old lady presented to dermatology with an 18-month history of erythematous macules affecting her arms, chest and thighs. A skin biopsy confirmed urticaria pigmentosa. She was asymptomatic at the time with no bony pain, gastrointestinal symptoms or mediator symptoms. She had a past history of anaphylactic reaction to alcuronium. There was no lymphadenopathy or hepatosplenomegaly clinically and her baseline results are shown in Table VI. She declined a BM biopsy. She was kept under review and remained asymptomatic. Twelve months from diagnosis the patient developed dyspepsia and flushing symptoms and a BM biopsy showed mast cell infiltrates (45% disease bulk) and evidence of fibrosis. Her peripheral blood film was normal and her BM aspirate showed 10–12% spindle-shaped mast

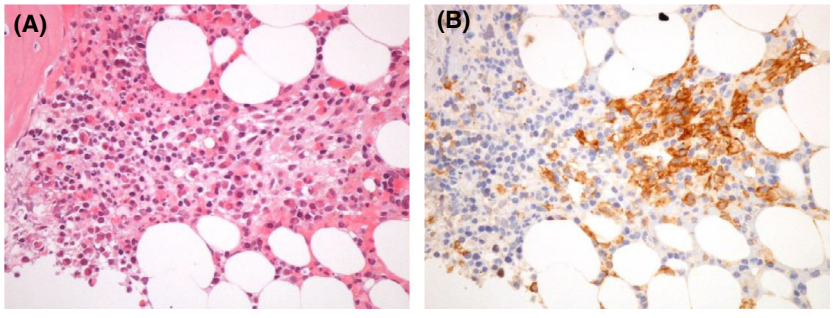


**Fig 4.** Low-disease bulk in systemic mastocytosis (SM) (case B). (A) Bone marrow biopsy showing 5–7% involvement by SM. H&E, (B) CD117.

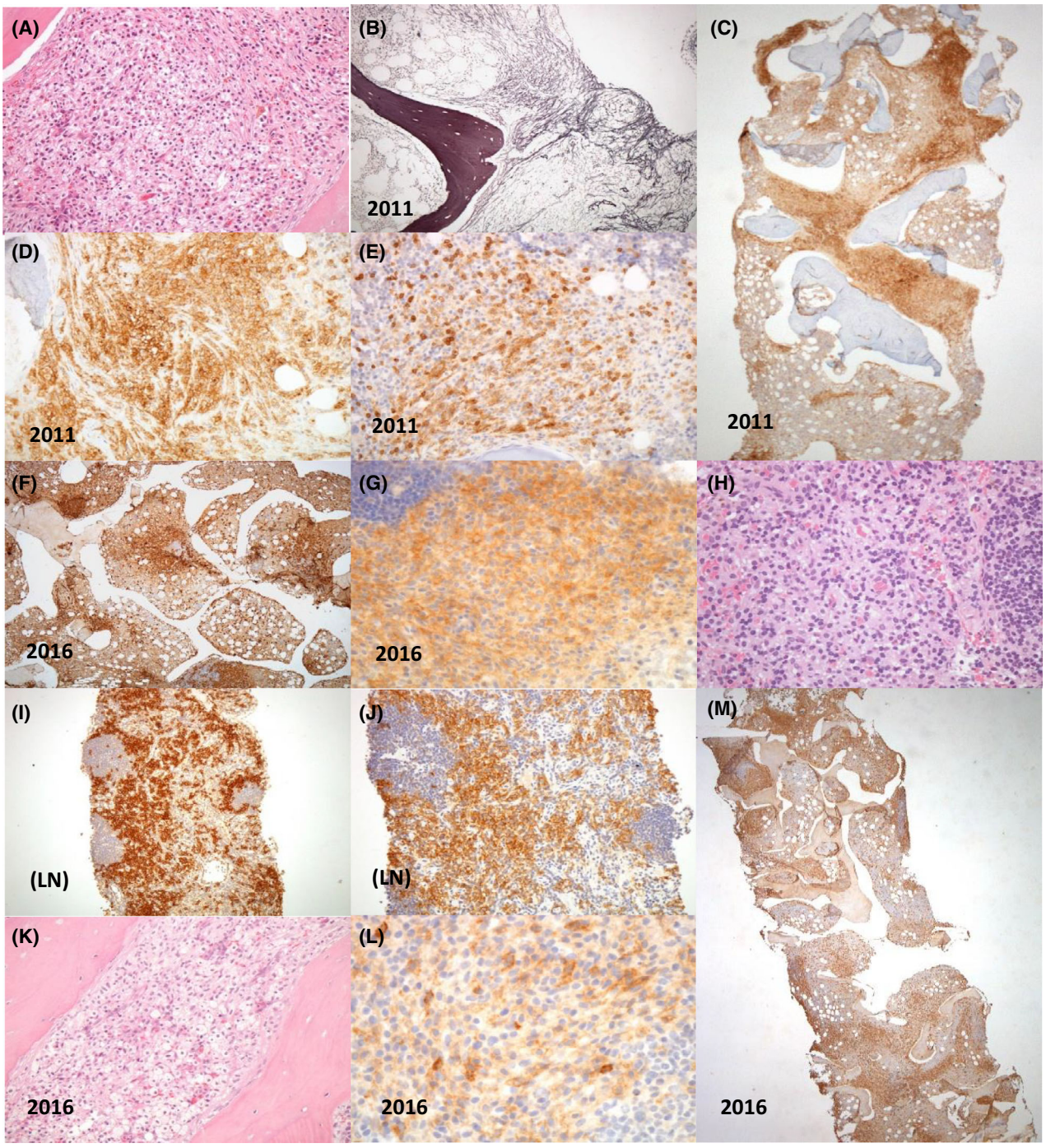


**Fig 5.** Smouldering systemic mastocytosis (Case C). Bone marrow from 2011, (A). H&E 20×. (B) Paratrabecular reticulin fibrosis. (C) CD117 showing 30% disease bulk. (D) CD25. (E) CD2. Bone marrow from July 2016 showing increased disease bulk – 40%. (F) MCT. (G) There is now co-expression of CD123. Retroperitoneal lymph node biopsy from 2016 showing lymph node involvement by mastocytosis. (H). H&E. (I) CD117. 5J. CD25. Bone marrow from Oct 2016 showing further increase in disease bulk to 50%. (K) H&E. (M) CD117. (L) The mast cells aberrantly express CD30.

cells. The patient was diagnosed with SSM. Ten years after her diagnosis, this patient continues to remain minimally symptomatic, has undergone successful operations for unrelated medical conditions and now has a palpable spleen. In this case, high serum tryptase levels correlated with high disease bulk, but this was not associated with a more severe disease course. This case reflects the overlap in spectrum between ISM and SSM.

**Table VI.** Results of investigations and clinical findings taken at diagnosis.

| | October 2007 |
|---|---|
| Full blood count | |
| Haemoglobin, g/l | 129 |
| WCC, $\times 10^9$/l | 6·6 |
| Neutrophils $\times 10^9$/l | 3·0 |
| Eosinophils, $\times 10^9$/l | 0·3 |
| Platelets, $\times 10^9$/l | 297 |
| Liver and bone profile | |
| Bilirubin μmol/l | 12 |
| ALT IU/l | 17 |
| ALP IU/l | 156 |
| Albumin g/l | 45 |
| Corr. Ca mmol/l | 2·22 |
| Specialist tests | |
| BMT disease bulk | 45% |
| Serum tryptase (μg/l) | 174 |
| *KIT* | D816V positive |
| Clinical features | |
| Splenomegaly | 13 cm on ultrasound |
| Hepatomegaly | None |
| DEXA scan | Osteopenia |

*Pathology (October 2007).* The BM shows 45% involvement by paratrabecular and interstitial infiltrates of spindle-shaped mast cells (Fig 6). There is evidence of interstitial fibrosis, with pronounced paratrabecular fibrosis in the areas of mast cell involvement. The mast cells express CD25 and CD2.

*Practice points: SSM.* Distinguishing SSM from ISM at one end of the spectrum and ASM or mast cell leukaemia (MCL) at the other end needs careful clinical and histological assessment.

Patients with SSM may be asymptomatic or minimally symptomatic, despite the high mast cell burden.

### *Systemic mastocytosis with an associated haematological neoplasm (SM-AHN)*

*Introduction.* SM is a clonal stem cell disease, and the potential for other lineages to develop clonal aberrations is therefore not surprising. The *KIT* D816V mutation has been clearly demonstrated in cell lineages other than mast cells within the BM of patients with SM (Taylor et al., 2004; Frederiksen et al., 2016). The AHN may precede, be concurrent with or follow the presentation and diagnosis of SM. AHNs span the entire spectrum of haematologic malignancies, including MDS/MPN (myelodysplastic syndromes/myeloproliferative neoplasms) overlap syndromes (CMML being the commonest), MDS, AML, and less commonly lymphomas and plasma cell neoplasms.

### *Case E*

A 60-year-old female was evaluated for erythrocytosis and thrombocytosis following a routine GP review. While a history of allergy to crab meat and penicillin was noted, she did

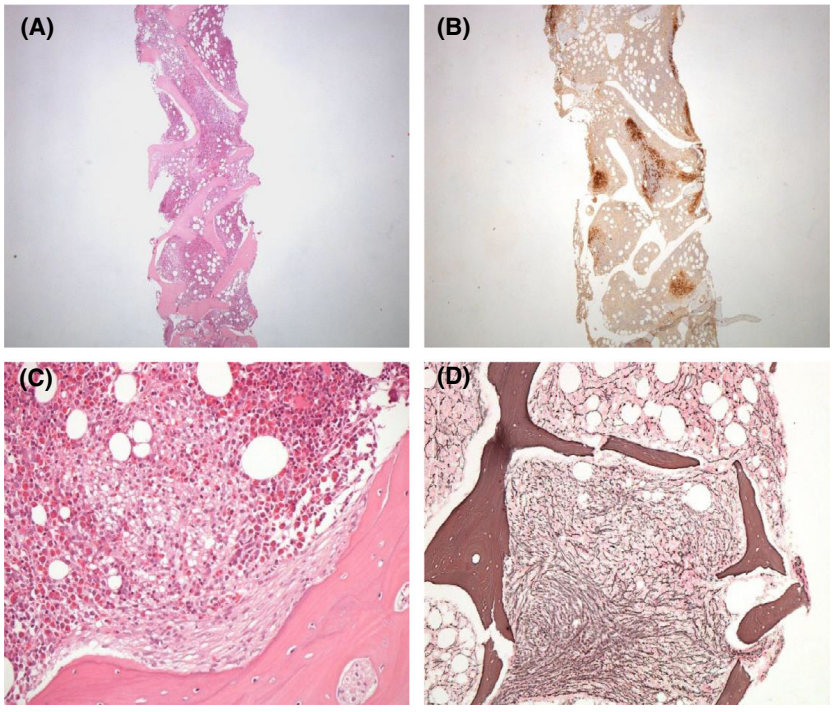


**Fig 6.** Smouldering systemic mastocytosis (Case D). Bone marrow biopsy showing paratrabecular zones of fibrosis containing mast cells. (A) H&E 2×. (B) CD117. (C) H&E 20×. (D) Reticulin stain showing increased reticulin fibrosis.

**Table VII.** Results of investigations and clinical findings taken at diagnosis.

| | 2005 |
|---|---|
| Full blood count | |
| Haemoglobin, g/l/PCV | 157/0·458 |
| WCC, $\times 10^9$/l | 11·7 |
| Neutrophil count, $\times 10^9$/l | 7·9 |
| Eosinophil, $\times 10^9$/l | 0·1 |
| Platelets, $\times 10^9$/l | 510 |
| Liver and bone profile | |
| Bilirubin μmol/l | 6 |
| ALT IU/l | 19 |
| ALP IU/l | 70 |
| Albumin g/l | 43 |
| Corr. Ca mmol/l | 2·30 |
| Specialist tests | |
| Disease bulk | <2% |
| Serum tryptase (μg/l) | 15 |
| *KIT* | D816V positive |
| Clinical features | |
| Splenomegaly | None |
| Hepatomegaly | None |
| DEXA scan | Osteopenia |

**Table VIII.** Results of investigations and clinical findings taken at diagnosis and reassessment.

| | Year | |
|---|---|---|
| | March 2015 | May 2016 |
| Full blood count | | |
| Haemoglobin, g/l | 124 | 138 |
| WCC, $\times 10^9$ | 7·1 | 8·0 |
| Neutrophil count, $\times 10^9$ | 2·9 | 2·7 |
| Monocyte count, $\times 10^9$ | 1·5 | 2·6 |
| Eosinophil, $\times 10^9$ | 0·4 | 0·6 |
| Platelets, $\times 10^9$ | 202 | 258 |
| Liver and bone profile | | |
| Bilirubin | 6 | 8 |
| ALT | 34 | 14 |
| ALP | *241* | *239* |
| Albumin | 45 | 37 |
| Corr. Calcium | 2·21 | 2·33 |
| Specialist tests | | |
| BMT disease bulk | | 5–10% |
| Serum tryptase (μg/l) | 100 | 125 |
| *KIT* | | D816V positive |
| Myeloid gene panel | | TET2 mutation allele burden 29% |
| Clinical features | | |
| Splenomegaly | 15·4 cm (ultrasound) | 15·5 (on PET) |
| Hepatomegaly | None | None |
| DEXA result | Osteopenia | |

not have any gastrointestinal or mediator-associated symptoms. Examination showed no rash and no palpable lymphadenopathy or hepatosplenomegaly. Her blood results are shown in Table VII. She was found to be negative for the *JAK2* V617F mutation, had normal ferritin and ESR but a raised carboxyhaemoglobin level of 6·3%. She proceeded to have a BM biopsy which confirmed a diagnosis of essential thrombocythaemia, with an incidental finding of a small clonal mast cell population. A diagnosis of SM-AHN (ISM+ET) was made at that time. She was started on aspirin. A baseline DEXA scan confirmed osteoporosis and she was started on Adcal-D3.

In 2012, seven years after her initial presentation, she developed an urticarial rash which was confirmed as urticaria pigmentosa on skin biopsy; she still had minimal symptoms which infrequently required antihistamine therapy.

This case demonstrates the common association between SM and myeloproliferative neoplasms, and in this case the former was an incidental finding in an originally asymptomatic patient.

*Pathology.* The BM biopsy from March 2006 (Fig 7A–D) is mildly hypercellular, showing relatively reduced erythropoiesis, with increased megakaryocytes forming loose groups and including some with staghorn nuclei. CD117 staining highlights a focal increase in mast cells (<2% of marrow cells), both spindle-shaped and round forms around bone and blood vessels, with the mast cells showing aberrant expression of CD25. The appearances are of SM-AHN, the AHN component being essential thrombocythaemia.

### *Case F ( Table VIII results)*

This 68-year-old lady presented with a five-year history of a rash affecting her face, chest and thighs. A skin biopsy confirmed the presence of mast cells. She reported diarrhoea and lethargy. There was no history of bony pain, flushing or atopy. Clinical examination revealed no lymphadenopathy but there was palpable splenomegaly, which was confirmed on ultrasound. The severity of the patient's diarrhoeal symptoms prompted a colonoscopy, and a colonic biopsy confirmed the presence of mast cells. Her serum tryptase was 100 μg/l. A diagnosis of ISM was made.

Thirteen months after diagnosis, the patient developed significant ascites, requiring paracentesis. An upper gastrointestinal endoscopy revealed gastric and duodenal varices. This was accompanied by a rise in her serum tryptase to 125 μg/l. A BM examination was performed and showed 5–10% mast cells with evidence of CMML-1. Her monocyte count at this time was $2{\cdot}6 \times 10^9$. The diagnosis was changed to SM and CMML-1, therefore SM-AHN.

The patient required paracentesis and was treated with steroids for the subsequent two months, at which point midostaurin 100 mg BD (twice daily) was started on a compassionate use programme. She had an excellent clinical

**Table IX.** Results of investigations and clinical findings.

| | At trial entry (2012) | Reassessment (2012) | Reassessment (2015) |
|---|---|---|---|
| Full blood count | | | |
| Haemoglobin, g/l | 84 | 104 | 113 |
| WCC, $\times 10^9$/l | 5·9 | 5·3 | 5·0 |
| Neutrophil count, $\times 10^9$/l | 3·4 | 3·5 | 3·8 |
| Eosinophil, $\times 10^9$/l | 0·2 | 0·1 | 0·1 |
| Platelets, $\times 10^9$/l | 130 | 195 | 148 |
| Liver and bone profile | | | |
| Bilirubin μmol/l | 15 | 7 | 8 |
| ALT IU/L | 15 | 19 | 24 |
| ALP IU/L | 154 | 147 | 75 |
| Albumin g/l | 44 | 44 | 49 |
| Corr. Ca mmol/l | 2·23 | 2·22 | 2·30 |
| Specialist tests | | | |
| BMT disease bulk | 60–70% | 30–35% | 40% |
| Serum tryptase (μg/l) | 271 | 137 | 101 |
| *KIT* | Positive-D816L | | |
| Clinical features | | | |
| Splenomegaly | 22 cm* | 21 cm* | 18·6 cm* |
| Hepatomegaly | 2 cm below costal margin (not recorded on CT) | 19·5 cm* | 19·2 cm* |
| DEXA scan | Normal | Normal | Normal |

*Craniocaudal measurement via CT.

response with resolution of ascites, lethargy and significant improvement in her rash, with cessation of steroids. There has not however been any radiological improvement on positron emission tomography (PET) scanning, with no reduction in bowel thickening, abdominal lymph node or spleen size, or bony changes.

In August 2017, she progressed clinically with ascites which was refractory to diuretic treatment, requiring weekly paracentesis and progressive anaemia. A liver biopsy confirmed clonal mast cell infiltration. In November 2017, she consented to be enrolled onto a phase 1 clinical trial using Avapritinib.

*Pathology.* Biopsies from the colon (Fig 8A–C; October 2015) show a subtle but significant mast cell infiltrate (with sparing of the rectum), including aggregates of >15 mast cells. The infiltrating mast cells express CD25. The subsequent BM (Fig 8D–H; May 2016) is markedly hypercellular, with expanded granulopoiesis, variable eosinophilia, and some megakaryocyte atypia. CD14 highlights increased monocytes. Atypical, spindle-shaped mast cells form peri-trabecular aggregates and account for 5–10% of nucleated marrow cells; the mast cells show aberrant expression of CD25, CD2, CD30 and CD123. The appearances are of SM and CMML1, therefore the pathology fits the category of SM-AHN.

The AHN component in this subtype may be diagnosed concurrently with SM (Case E), or in some cases may precede or follow the diagnosis of SM (Case F). Where the AHN component is more prominent, it is important not to overlook SM.

The diagnosis of an AHN is prognostically significant, since it determines the patient's prognosis (Naumann et al., 2016). Patients with AHN and additional secondary mutations have a poorer prognosis. Patients who harbour *SRSF2, ASXL1 and RUNX1* mutations in addition to *KIT* D816V ('SAR' mutations) have a significantly reduced overall survival rate (Schwab et al., 2013). The development of recent clinical molecular prognostic models (Naumann et al., 2016; Pardanani et al., 2016; Jahwar et al., 2019) have led to the routine use of myeloid gene panels to help prognosticate patients and guide therapy.

*GI Involvement in systemic mastocytosis.* Histologically, gastrointestinal involvement by SM shows a broad spectrum of changes (Shih et al., 2016); the disease process may be multifocal, and involvement may be subtle, in which case sampling error is always a possibility. When mast cell burden is low, aberrant CD25 expression is helpful in demonstrating a neoplastic population of mast cells. Aggregates of >15 mast cells in the GI tract fall within the definition of SM (major criterion). However, enumeration of more diffuse infiltrates, and their distinction from a normal population of GI mucosal mast cells may be more difficult. Attempts have been made to quantify mucosal mast cells in SM and diarrhoea. Mucosal mast cells can be increased in non-clonal diarrhoeal

**Table X.** Results of investigations and clinical findings taken at diagnosis.

| | |
|---|---|
| Full blood count | |
| Haemoglobin, g/l | 113 |
| WCC, $\times 10^9$/l | 18·6 |
| Neutrophil count, $\times 10^9$/l | 9·9 |
| Eosinophil, $\times 10^9$/l | 4·7 |
| Platelets, $\times 10^9$/l | 99 |
| Blood film | Leucoerythroblastic with 1% circulating mast cells. |
| Liver and bone profile | |
| Bilirubin μmol/l | 10 |
| ALT IU/l | 55 |
| ALP IU/l | 683 |
| Albumin g/l | 39 |
| Corr. Ca mmol/l | 2·36 |
| Specialist tests | |
| Bone marrow aspirate | 23–25% round mast cells present |
| BMT disease bulk | 40% |
| Cytogenetics | Normal |
| Serum tryptase (μg/l) | *514* |
| *KIT* | D816V positive |
| Myeloid gene panel | |
| GATA2 (47% allele burden) | |
| SRSF2 (54% allele burden) | |
| ASXL1 (38% allele burden) | |
| RUNX1 (44% allele burden) | |
| Clinical features | |
| Splenomegaly | Palpable 16 cm below costal margin |
| Hepatomegaly | Palpable 9 cm below costal margin |
| DEXA scan | ND |

ND, not determined.

illnesses (Doyle et al., 2014), with the mean mast cell infiltrate (per high power field) significantly greater in SM, but this is highly variable and overlaps with non-SM pathologies. Intra-mucosal mast cells may be increased in patients with diarrhoea and IBS-type symptoms; however, confirmation of bowel involvement by SM requires documentation of an immunophenotype normally associated with clonal mast cells.

*Practice points: SM-AHN.* It is very important to carefully assess the full blood count, differential and background haematopoiesis in all cases of SM to investigate the possibility of an AHN, with CMML being the most common associated haematologic neoplasm.

A myeloid gene panel is useful in evaluating prognosis at baseline in SM-AHN.

In patients where there is doubt over the aetiology – whether it is the SM or AHN component which may be causing the organ damage – then biopsy of the organ should be considered to guide treatment.

The AHN component often determines the patient's prognosis, and therefore recognition and correct classification is critical to enable appropriate management.

### *Aggressive mastocytosis (ASM)*

*Case G ( Table IX results).* A 26-year-old female was referred in 2012 for consideration of single agent midostaurin in the context of a single arm phase 2 clinical trial for patients with ASM (Gotlib et al., 2016). She had a very unusual history in being diagnosed at the age of four with a persistent rash which had been present since birth, along with hepatomegaly. A diagnosis of urticaria pigmentosa was confirmed on skin biopsy and SM on BM biopsy at the time. She had minimal symptoms needing intermittent antihistamines only and was under regular review. On review in 2011, she was more symptomatic and becoming anaemic. A trial of Interferon α was of little benefit with associated side effects. She was monitored and started to need red cell support to manage her anaemia. She was eligible and consented to start treatment with midostaurin 100 mg BD, to which she had a good clinical response with almost complete resolution of her rash over a three-year period (Fig 9), no palpable organomegaly and normalisation of her blood counts. She remains on midostaurin at present.

The initial BM biopsy in March 2012 (Fig 9D) shows 60–70% involvement by SM, in the form of interstitial nodules and juxta-trabecular aggregates of spindle-shaped mast cells, as well as singly dispersed spindle-shaped mast cells. The mast cells showed aberrant expression of CD25, CD30 and CD123, with focal expression of CD2. There is a change in morphology of the clonal mast cells over time with exposure to midostaurin with loss of clonal markers, as shown in Figs 10 and 11.

*Practice points: ASM.* Case G has been closely monitored, as required, by participating in a clinical trial of a targeted therapeutic agent. Her repeated BM trephines have shown variable disease bulk over time despite clinical response. Disease burden maybe variable and as sites of BM biopsies vary, the disease burden will too.

The immunophenotype of the mast cells has varied following treatment with midostaurin, raising the possibility of eradication of clones harbouring those markers.

The change in shape from spindle to round hypergranulated mast cells is being noticed more frequently in a post-therapy setting.

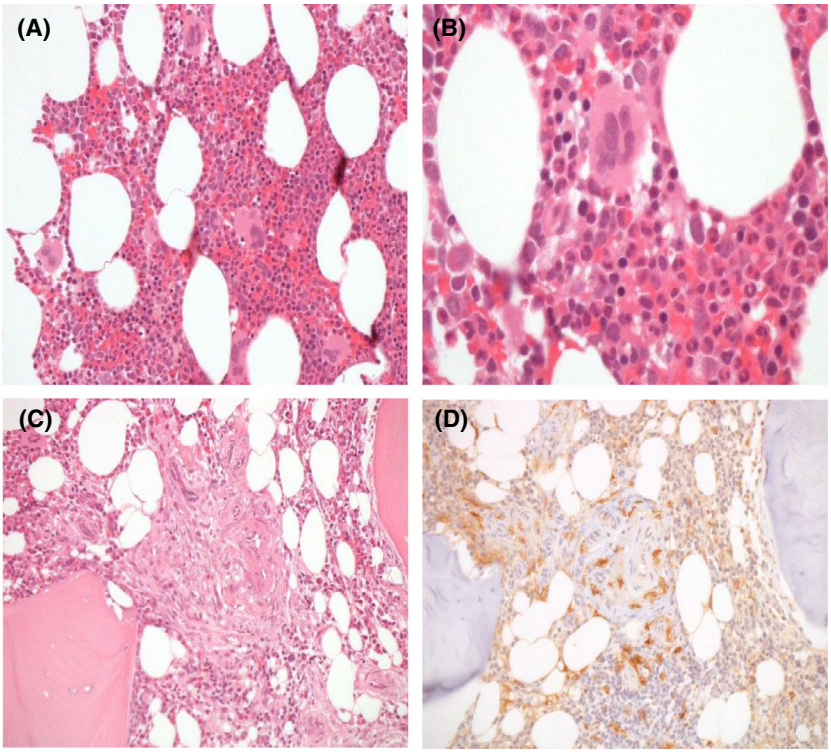


**Fig 7.** SM-AHN [SM-ET] (Case E). (A) Bone marrow showing increased numbers of large megakaryocytes, H&E 4×. (B) Hyperlobated megakaryocyte typical of ET, H&E 20×. Mast cell aggregates, (C) H&E 10×, (D) CD117.

All patients with advanced SM should have a baseline myeloid gene panel.

A holistic approach to interpreting clinical, histopathological and molecular features is needed to guide prognosis and treatment.

In many cases, *KIT*-targeted therapies demonstrated an improvement in cutaneous lesions when seen in ASM, and when the disease responds to the drug.

### *Mast cell leukaemia (MCL)*

*Introduction.* Mast cell leukaemia is defined by the WHO (Valent et al., 2001; Arber et al., 2016; Valent et al., 2017) as an aggressive variant of SM in which mast cells make up at least 20% of nucleated cells on a *bone marrow aspirate* – these are usually immature morphologically. Two variants are recognised – aleukaemic (peripheral blood mast cells <10%) and leukaemic (peripheral blood mast cells >10%). MCL may arise secondary to existing SM, or may arise *de novo*. The *KIT* D816V mutation is seen less frequently in MCL than in other subtypes of SM (Jawhar et al., 2017). MCL may occur with an AHN, although the reported incidence of this varies in the literature from <10% to >70% (Georgin-Lavialle et al., 2013; Jawhar et al., 2017). While MCL is known to have a very aggressive course (life expectancy <1 year), leukaemic presentations with a more indolent course have been described. These patients lack C-findings (organ involvement with organ dysfunction) and the mast cells have a more mature appearance on morphology. These patients are labelled as having chronic MCL to differentiate them from the more aggressive variant which is known as acute MCL (Valent et al., 2015).

### *Case H (Table X results)*

This 64-year-old male with MCL was referred for consideration of eligibility for a phase 1 clinical trial. He had no significant past medical history of note and had been previously well. He presented with a three-month history of weight loss (>10% baseline body weight), drenching night sweats, anorexia and severe fatigue. He had noticed a change in his bowel habits with loose stools up to twice a day and an increase in reflux. Examination revealed muscle-wasting and significant hepatosplenomegaly, but no peripheral palpable lymphadenopathy. There was no evidence of cutaneous mastocytosis. This is a case of *de novo* aleukaemic mast cell leukaemia. MCL accounts for <1% of all cases of mastocytosis and is known to have a poor prognosis with a median overall survival of less than six months. He consented to participate in the phase 1 BLU 285 trial for patients with ASM.

*Pathology.* The diagnosis of aleukaemic MCL was made on the basis of only 1% circulating mast cells in peripheral blood (Fig 12A), the bone marrow aspirate showing 25% immature round granulated mast cells (Fig 12B), and the

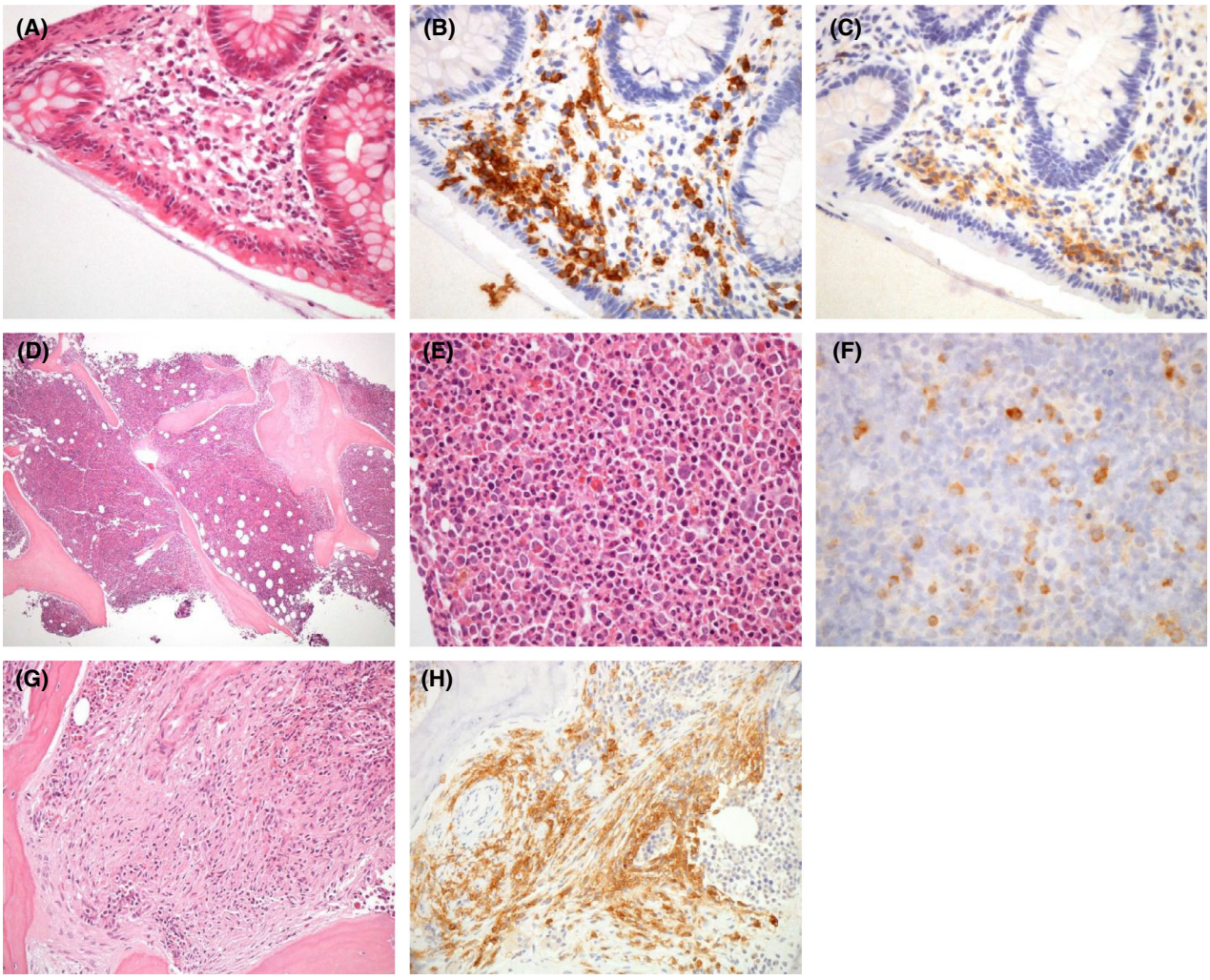


**Fig 8.** SM-AHN progressing to ASM (Case F). Colon (2015) showing lamina propria infiltrates of neoplastic mast cells. (A) H&E, (B) CD117, (C) CD25. Bone marrow (2016) shows a hypercellular marrow with increased monocytes (CMML-1). (D, E) H&E, (F) CD14. Mast cell aggregates with fibrosis are clearly seen. (G) H&E, (H) CD117.

bone marrow trephine biopsy showing hypercellularity, with around 40% of nucleated marrow cells being mast cells. The majority of the mast cells are round, arranged either as interstitial aggregates or singly dispersed within the interstitium. They show aberrant expression of CD25, CD30 with patchy weak expression of CD123.

*Practise points: mast cell leukaemia.* The bone marrow aspirate is pivotal in making a diagnosis of MCL (>20% mast cells).

MCL can be aleukaemic (peripheral blood <10% mast cells) or leukaemic (>10% circulating mast cells).

Acute MCL is defined by immature morphology and an aggressive course. Chronic MCL is defined by mature mast cell morphology and an indolent course.

Mast cells in MCL tend to be immature and lose the spindle shape conventionally seen in ISM.

Morphologic variants include a spectrum from blast-like, round to spindle-shaped cells with varying degrees of granularity. Some forms may have coarse purple granules (Georgin-Lavialle et al., 2013; Valent et al., 2015; Swerdlow et al., 2017).

Patients with MCL have the poorest overall survival (Pardanani et al., 2016) and should be considered for trials using newer targeted agents, high dose chemotherapy and bone marrow transplant if clinically eligible.

## Bone marrow pathology summary

The percentage of neoplastic mast cells in the BM (compared to all nucleated marrow cells), has been shown to

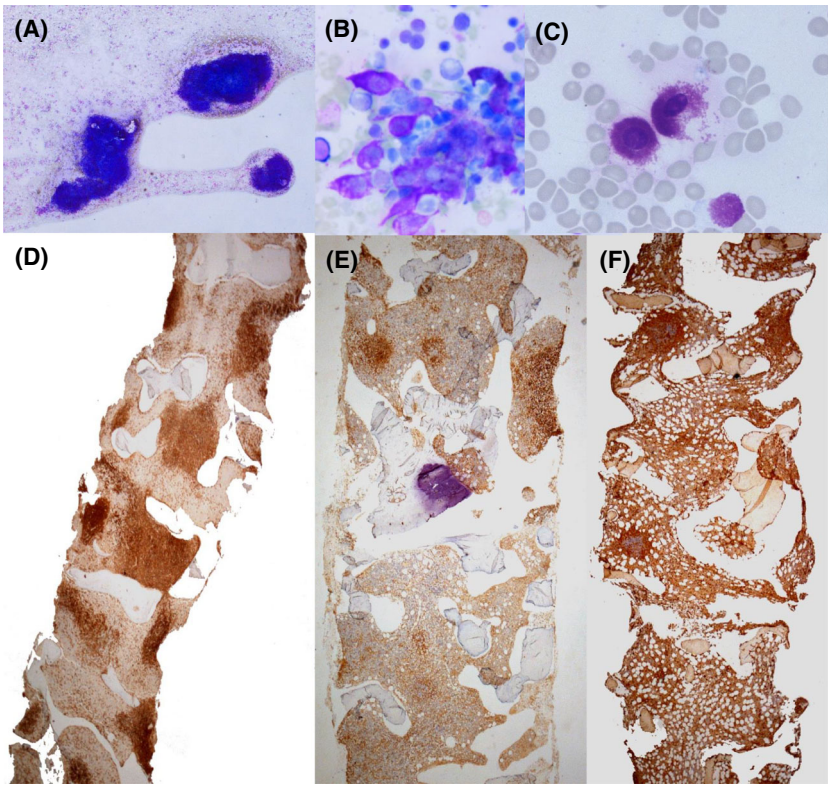


**Fig 9.** Aggressive systemic mastocytosis (Case G). Bone marrow aspirate showing clusters of mast cells. (A) (low power), (B) (high power). The mast cells are an admixture of spindle-shaped and round hypergranular forms (C). Bone marrow biopsies showing variable disease bulk across the years. (D) March 2012, 70%. (E) Sept 2012, 30%. (F) Dec 2015, 40%.

correlate with disease prognosis (Sperr et al., 2001). However, we have found that BM disease bulk is not always indicative of the patient's current clinical parameters. This highlights the fact that subtyping of SM is not possible on the basis of the BMT findings alone. Given that SM can show a variable distribution in the BM, sampling bias should always be considered if such a discrepancy arises, and the whole clinical picture taken into consideration, especially if there are other known sites of SM involvement.

It can be difficult to make a diagnosis if the neoplastic mast cells show only a paratrabecular distribution, with significant associated fibrosis (Case D).

CD25 and CD2 immunohistochemical staining is routinely used to identify aberrant expression in neoplastic mast cells, and their expression (CD25 and/or CD2) form one of the minor criteria for the diagnosis of SM (Swerdlow et al., 2017).

Although the typical appearance of SM in the BM is that of aggregates of spindle-shaped mast cells, occasionally the

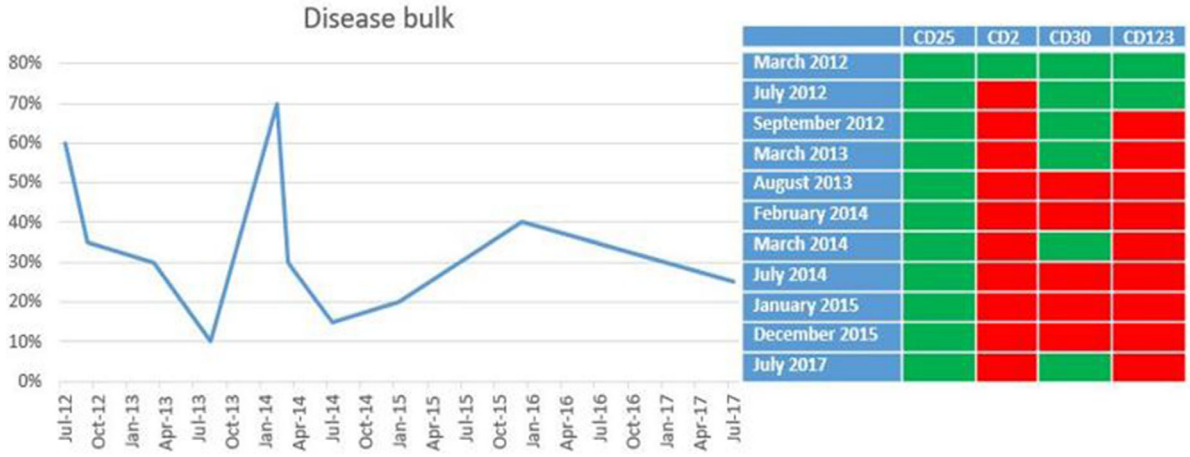


**Fig 10.** Bone marrow disease bulk over the years for case G, along with expression profile of mast cell markers by immunohistochemistry (green: expressed, red: negative).

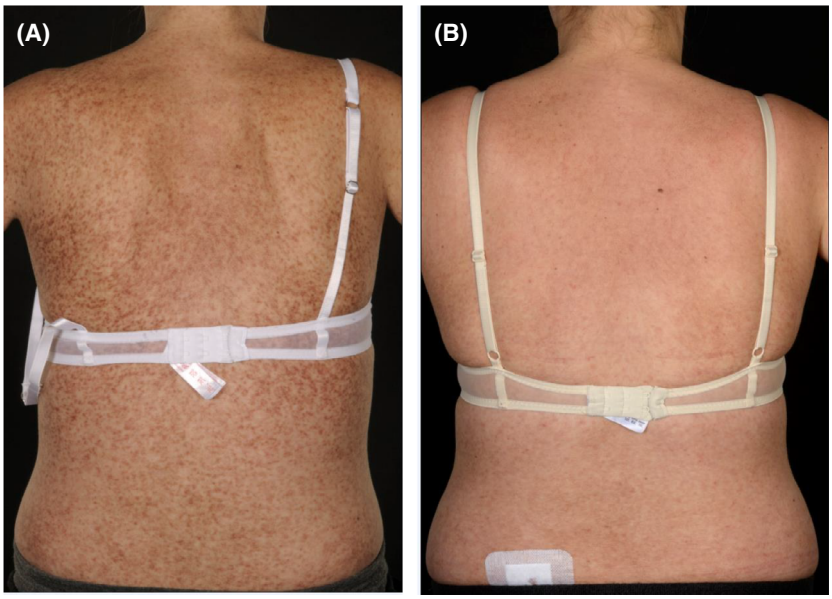


**Fig 11.** Aggressive systemic mastocytosis (Case G). Skin disease (A) Pre-treatment. (B) After treatment with midostaurin.

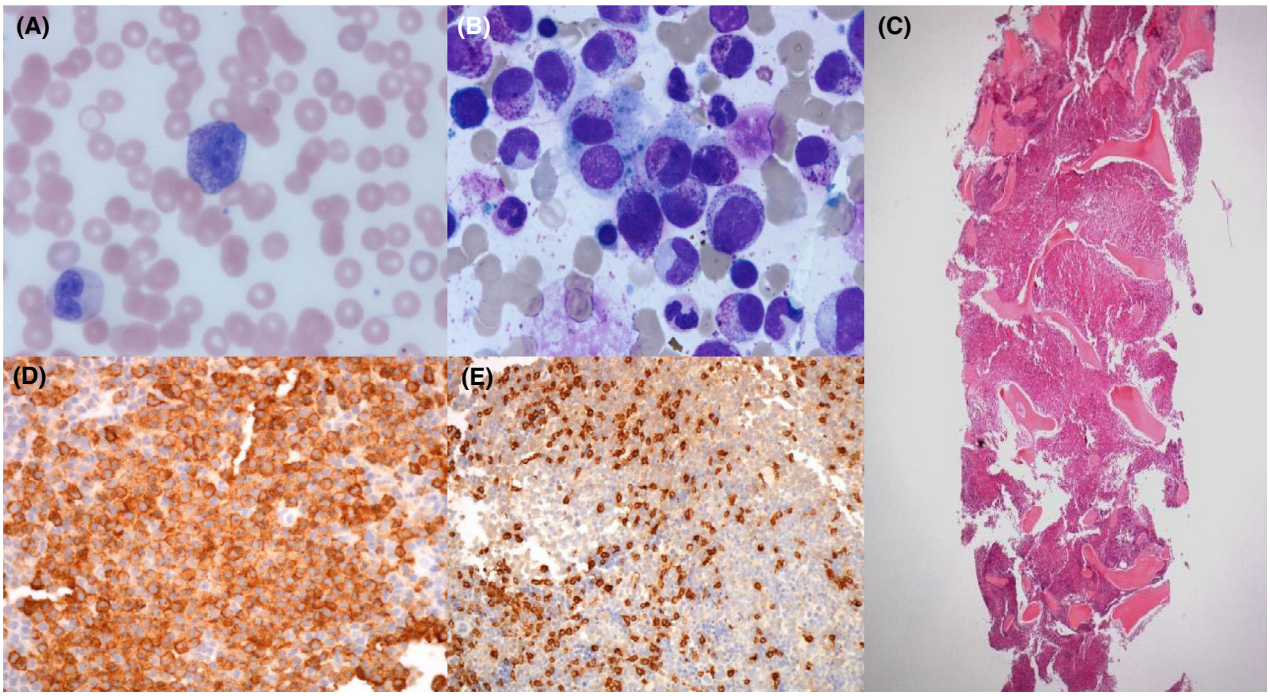


**Fig 12.** Mast cell leukaemia (Case H). (A) Circulating mast cell in peripheral blood (Oil 60×). (B) Immature round granulated mast cells in bone marrow aspirate (Oil 60×). (C) Hypercellular bone marrow biopsy. Nodules (D) and singly scattered round mast cells (E) within the bone marrow (mast cell tryptase IHC).

predominant feature may be singly dispersed mast cells, which are morphologically atypical with aberrant expression of CD25, highlighting the importance of immunohistochemical staining in identifying such a population.

In addition, aberrant expression of CD30 and CD123 have been increasingly recognised throughout the spectrum of SM pathologies. Both CD30 and CD123 expression has been reported to be associated with more aggressive disease (Sotlar et al., 2011; Valent et al., 2011; Blatt et al., 2015). This prognostic significance is not consistently reported in the literature (Morgado et al., 2013; Doyle et al., 2014) and in our experience, in a cohort of 43 patients (Moonim et al., 2012),

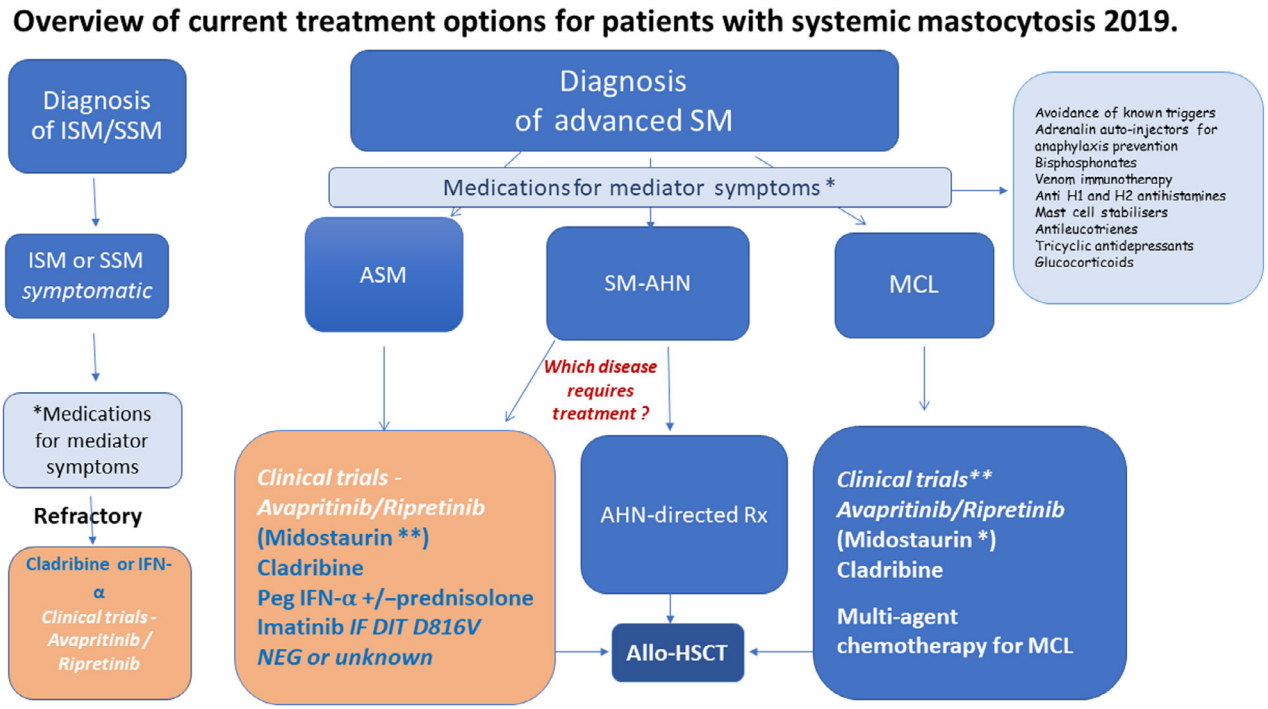


**Fig 13.** Overview of current treatment options for patients with SM 2019. *Combinations may be needed and doses higher than those recommended in the British National Formulary. **Midostaurin has been approved by the FDA/EMA for patients with advanced SM. It is currently under review by NICE in the UK.

we did not find direct association between CD30 and CD123 expression and aggressive behaviour. However, Moonim et al. (2012) did identify that CD30 expression correlated with higher disease bulk. In our practice, we have seen variability in aberrant antibody expression between sites of disease and over time. **Case C** (SSM) showed expression of CD123 but not CD30 in the first BMT, no expression of either antibody in the lymph node involved by SM, and focal expression of both antibodies in a subsequent biopsy.

## Pathology Practice Points

Although neoplastic mast cells are typically hypogranulated, hypergranulation may be seen, and does not exclude a diagnosis of SM.

Paratrabecular aggregates of mast cells can be associated with significant fibrosis, which may distract from the identification of neoplastic mast cells, especially when disease burden is low.

The distribution of neoplastic mast cells within the BM does not correlate with disease severity.

Although BM disease bulk has been shown to correlate with prognosis, this is not absolute, and does not distinguish SM subtypes.

ISM may show a highly variable distribution in the BM, sampling bias should always be considered if there is any discrepancy between BM findings and the full clinical picture.

*KIT* mutation testing at diagnosis should be carried out by allele-specific nested PCR technique as this is more sensitive than NGS.

NGS-based myeloid gene panels should be carried out in all cases of advanced SM. Additional somatic mutations are seen in approximately 90% of patients with advanced SM and predominantly in those with SM-AHN. The commonly seen mutations are TET2, SRSF2, ASXLI, EZHZ, CBL, RUNX1.

## CONCLUSIONS

Systemic mastocytosis is a rare haematological neoplasm with a spectrum of clinical manifestations, often unique to each patient. The diagnostic and classification pathways are complex. They highlight the need for accurate application of diagnostic criteria, setting up of diagnostic pathways, including molecular analysis with review of histology by experienced haematopathologists and management by clinicians with expertise in specialist comprehensive care centres. The current treatment options for patients with SM are

summarised in Fig 13. With novel targeted therapies entering clinical trial arenas, there is now hope for this orphan group of patients who frequently have a poor prognosis or severely impaired quality of life. It is vital we continue to work internationally and collaboratively to improve our understanding of the pathophysiology of this disease, impact of treatments and move towards truly personalised treatment.

## Acknowledgements

We would like to acknowledge the following members of our mastocytosis team: Dr C. Grattan, Professor C. N. Harrison, Dr D. McLornan, Dr N. Curto-Gracia, C. Woodley, Y. Frances, Dr Y. Miki, Dr. M Ong, Dr B. Wilkins, Dr J. van der Walt, D. Drasutyte, M. Ciesielska, T. Olaoni and Professor N. C. P. Cross.

## Author Contribution

All four authors DHR, AG, CO and MTM were responsible for all aspects of research, article preparation and writing.

## Conflicts of Interest

No conflicts of interest exist.

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