AMJ Australasian Medical Journal [AMJ 2016;9(7):215–220]

Systemic mastocytosis associated with minimal change disease

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CASE STUDY

Please cite this paper as: Amin T, Elias T, Otto S, Hamilton J. Systemic mastocytosis associated with minimal change disease. AMJ 2016;9(7):215–220.
http://doi.org/10.21767/AMJ.2016.2646

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ABSTRACT

Systemic Mastocytosis (SM) has not previously been reported in association with minimal change disease (MCD). Mastocytosis is a rare myeloproliferative disease that is characterised by uncontrolled proliferation of aberrant mast cells. This can lead to a wide variety of symptoms and can present as either a cutaneous or a systemic disease. Systemic manifestations usually include bone marrow, intestine, liver and splenic infiltration of mast cells, with reports of renal manifestations being rare. This is a case report of a 70-year-old man who was known to have Systemic Mastocytosis and who presented with nephrotic range proteinuria. Renal biopsy diagnosed Minimal Change Disease with mast cell infiltration being an identified by C-kit staining. The patient was treated with steroids and is currently in remission of the proteinuria.

Key Words
Mastocytosis, minimal change disease, proteinuria

Implications for Practice:

1. What is known about this subject?
Mastocytosis is a rare condition. It can affect different organs of our body, but renal association is not widely known.

2. What new information is offered in this case study?
This is the first case to report mastocytosis association with minimal change disease.

3. What are the implications for research, policy, or practice?
Patient with systemic mastocytosis may present with nephrotic syndrome and minimal change disease, which is generally well responsive to steroid treatment.

Background

Mastocytosis

Mastocytosis is a rare mast cell disorder that can present with diverse range of symptoms which include long history of urticaria pigmentosa followed by insidious onset of flushing, craping abdominal pain, diarrhoea, bone pain and hepatomegaly.[1] Physiologically, mast cells are a vital component of the innate immune system, originating from the pluripotent haematopoietic stem cell (CD-34 positive) and leaving the bone marrow to migrate to well vascularize tissues before maturation. Mast cells are commonly seen in the bone marrow, liver, spleen and lymph nodes, being most prominent in the tissues that form protective barriers, such as the skin and mucous membranes.[2] Pathologically, mast cells are one of the primary responders in allergic reactions, orchestrating strong immune responses to minute amounts of allergens.

Mast cells contain a wide range of biologically active substances called mast cell mediators. These include preformed mediators, lipid mediators, chemokine and growth factors.[1] Tryptase is one of the major protein components of mast cell secretory granules. It is kept inactive by low intracellular pH until exocytosis. Substrates of tryptase play an important role in the anticoagulant effect, vascular permeability and anaphylaxis.[3,4] The receptor for stem cell growth factor is KIT. This is a trans-membrane protein with intrinsic tyrosine kinase activity. It is expressed on a variety of cell types that include mast cells, hematopoietic progenitor cells, melanocytes, germ cells, and gastrointestinal pacemaker cells. It plays a pivotal role in cell regulation. The receptor of Stem Cell Factor for

mast cells is also designated as CD 117. The KIT gene that codes for CD 117 is situated on chromosome 4.[3]

In 2008, the World Health Organization (WHO) classified mastocytosis into two major groups: cutaneous mastocytosis (CM), with disease limited to the skin, and systemic mastocytosis (SM), a clonal and disseminated condition.[5]

WHO has recognised three variants of CM: maculopapular CM or urticaria pigmentosa, diffuse CM, and solitary CM. Darier sign can provide evidence for a clinical diagnosis of mastocytosis. Darier sign is considered positive when the affected skin becomes swollen, pruritic and erythematous after applying gentle friction. Histological diagnosis is made by skin biopsy of the affected area undergoing staining with Giemsa or immunohistochemical staining for tryptase and c-kit. Management of CM includes exclusion of systemic disease, avoidance of triggers for mast cell activators, administration of antihistamines with both H1 and H2 blockade, and topical glucocorticoids.

Systemic mastocytosis differs from CM; it consists of a group of disorders exhibiting excessive mast cell accumulation typically in the bone marrow or other extra-cutaneous tissues. Approximately 90 per cent of adult patients with skin lesions have evidence of systemic disease at the time of diagnosis[6,7]. There are four distinct forms of SM: Indolent SM, SM with an Associated Haematologic Non-Mast cell lineage disorder, aggressive SM and mast cell leukaemia.

Currently, there are no curative treatments for SM, however, the course of disease can be altered with interventions. The treatment options for SM are determined by “B” and “C” findings, with B findings defined as organ involvement without organ dysfunction and C findings defined as organ involvement with organ dysfunction. B findings indicate treatment with the mediator-targeting drugs such as antihistamine H1 and H2 blocker and C findings require cytoreductive or targeted drugs such as Imatinib (in absence of D816V), corticosteroid, INFα or other chemotherapeutic agents to alter the course of the disease.[3,7]

Minimal change disease

Minimal change disease (MCD) is the most common cause of the nephrotic syndrome (NS) in children and a major cause of NS in adults. MCD is characterised functionally by a severe defect in glomerular perm-selectivity and histologically by an absence of changes seen under light microscopy, diffuse effacement of foot processes on electron microscopy and the absence of immune deposits with immunofluorescence. The pathogenesis of MCD is unclear, although the accumulated evidence suggests that it is systemic T cell dysfunction that results in the production of a glomerular permeability factor, altering the basement membrane’s permeability to protein.[8] The majority of cases of MCD are currently considered to be idiopathic, however secondary causes include medications, malignancy, infection and allergens. It can also be secondary to other systemic disorders, such as autoimmune diseases. Glucocorticoids, cyclophosphamide and rituximab, which modify cell-mediated responses, are proven to be beneficial in the treatment of MCD.[8]

Case details

A 70-year-old Caucasian male was initially referred to a tertiary centre in 2010 with a history of skin rash involving the chest, back, abdomen and thighs. The rash was gradually progressing over five years. There had been no febrile episodes, weight loss, pruritus or sensory neuropathy. Other co-morbidities included long-standing severe gastro-oesophageal reflux disease, undifferentiated intermittent abdominal pain, constipation and a current smoking history of 50 pack years.

He had no history of hypertension, diabetes or cardiovascular disease. Family history was remarkable only for his sister being diagnosed with multiple sclerosis in her fifth decade.

Clinical examination revealed that he was afebrile with vital signs in the normal ranges. There was a discrete, macular, violaceous, non-blanching rash, extending over his trunk with a positive Darier sign. The remainder of the systematic examination was unremarkable; specifically, there was no palpable lymphadenopathy, hepatosplenomegaly or neuropathy. Laboratory investigation including complete blood examination, electrolytes, renal function, liver function, serum albumin, lipid profile was unremarkable except serum tryptase was elevated at 118u/L. Urine microscopy showed no blood or protein.

Skin biopsy was consistent with cutaneous mastocytosis, with more than 15 per cent infiltration of mast cells aggregates. Bone marrow trephine demonstrated two concerning areas of marrow involvement of mast cells, with atypical cells, increased fibrosis and demonstration of CD25 and C-kit positivity. The C-kit mutation identified was A2447T (D816V mutation).

Gastroscopy identified reflux oesophagitis, duodenitis and a hiatus hernia. Duodenal biopsy demonstrated normal mucosa under light microscopy. An immunohistochemical CD117 stain identified mast cell involvement in the duodenum (Figure 1).

The diagnosis of SM with B findings was made on the basis of one major criterion and three minor WHO criterions. Major criteria include, more than 15 per cent infiltration of mast cells in the skin and minor criteria includes i) detection of an activating point mutation at codon 816 of *KIT* in bone marrow, ii) Mast cells in bone marrow express CD25, iii) serum total tryptase persistently exceeds 20ng/mL. However, partly due to patient choice and partly due to toxicities of the treatments used in SM with B findings, he was managed conservatively with topical steroids, loratadine, famotidine, and pantoprazole, with limited effect.

In July 2011, he presented with worsening shortness of breath and leg swelling, with examination revealing the known, persistent rash, new bi-basal lung crepitation and new bilateral pitting oedema in the lower limbs.

Investigations revealed hypoalbuminaemia (16g/L) and deranged lipid studies (cholesterol 12.8mmol/L, triglycerides 2.9mmol/L, LDL 9.5mmol/L, HDL 2mmol/L). Serum tryptase was again raised (127µg/L). Urinalysis showed normal specific gravity, no red blood cells and a large quantity of protein. A 24-hour urine collection revealed protein excretion of 5.8gm/day. The full blood count, serum electrolytes, urea, creatinine, liver function tests, blood glucose level, prostate specific antigen, serum protein panel, serum light chains, vasculitic and autoimmune screens were non-contributory.

Renal US and CT of the neck, chest and abdomen showed no significant pathology, specifically there was no lymphadenopathy, hepatosplenomegaly or any cystic lesions in the liver or kidney.

He underwent a renal biopsy (Figure 2). On the interstitium demonstrated a mild chronic inflammatory infiltrate, consisting largely of lymphocytes and was mildly fibrosed. Immunofluorescence was essentially negative apart from mild C3 staining within vessels. Electron microscopy showed hyperplasia of podocytes, with the foot processes being almost completely flattened and demonstrable microvillus transformation. No electron-dense deposits were detected. These findings were consistent with minimal change disease. C-kit staining of the renal biopsy identified aberrant mast cells.

Clinical course

The patient was treated with prednisolone 60mg daily and improved symptomatically. Four weeks later, he achieved remission of nephrotic range proteinuria and the serum albumin normalized. There was a mild improvement of his rash, but no change in his gastro-oesophageal reflux symptoms, abdominal pain or constipation for the duration of the course of prednisolone. The prednisolone was slowly tapered over the next six months.[9] Ten months after discontinuation of prednisolone, the spot urine albumin creatinine ratio and serum creatinine has remained normal and the patient was in complete remission.

Discussion

Systemic mastocytosis (SM) is a rare condition; hence the association of SM and renal disease is also rarely reported. Only three cases of SM associated with glomerulonephritis, with or without nephrotic syndrome, have been reported to date. The first case was described in 1983; a patient with SM developed mesangial glomerulonephritis with hyaline sclerosis and nephrotic syndrome.[10] The second case was described in 1988; SM associated with nephrotic syndrome (proteinuria of 4.75gm/24hrs). Renal biopsy was consistent with membranous nephropathy; no mast cell infiltration has been reported in the glomerulus. He was treated with prednisolone and chlorambucil with near completion recovery and remains stable up to 10 months post treatment till the case was reported.[11] A third case was reported in 2011; SM associated with mesangioproliferative glomerulonephritis and monoclonal gammopathy of undetermined significance, without the presence of nephrotic syndrome (proteinuria of 492.7mg/24hrs). Renal biopsy was consistent with mesangioproliferative glomerulonephritis; no mast cell infiltration has been reported in the glomerulus. The patient was treated with prednisolone and chemotherapy (IFN-α and cladribine) with partial respond. She was haemodialysis dependent all through and died 24 months from the initial diagnosis, secondary to sepsis.[12]

In our case, patient with SM presented with heavy proteinuria and renal biopsy showed MCD with infiltration of aberrant mast cells. Although the mast cell infiltration in the glomerulus did not fulfil WHO major criteria of diagnosis of extra-cutaneous SM (Multifocal, dense infiltrates of >15 per cent mast cells in sections of other extra-cutaneous organ), but we believe that it was significant enough to cause the disease. A small number of mast cell infiltrations

can be found in the normal kidney, but mostly found in diseased kidney with leukocytes infiltration and in tubulo-interstitial nephritis associated with progressive fibrosis and renal failure,[13–15] but in our case the renal biopsy showed aberrant mast cell invasion in the glomerulus without any tubulo-interstitial disease or leukocyte infiltrations.

Our patient was treated with high dose prednisolone with complete remission and the patient has remained in remission ten months post-completion of treatment.

Conclusion

To our knowledge, this is the first case to report the association of SM and MCD where significant amount of aberrant mast cell invasion was found in the glomerulus without any leukocytes infiltration or tubulo-interstitial disease. He was treated with high dose prednisolone with complete remission and remained in remission ten months post-completion of treatment.

References

1. Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009 Jun 4;113(23):5727–36.
2. Andersen CL, Kristensen TK, Severinsen MT, et al. Systemic mastocytosis – a systematic review. Dan Med J. 2012 Mar 1;59(3):A4397.
3. Metcalfe DD. Mast cells and mastocytosis. Blood. 2008;112:946–56.
4. Hallgren J, Pejler G. Biology of mast cell tryptase. An inflammatory mediator. Febs Journal. 2006 May 1;273:1871–95.
5. Horny HP, Metcalfe DD, Bennet JM, et al. Mastocytosis. In: WHO classification of tumours of haematopoietic and lymphoid tissues, 4th ed, Swerdlow SH, Camp E, Harris NL, et al (Eds), IARC, Lyon 2008.
6. Wolff K. Treatment of Cutaneous Mastocytosis. International archives of allergy and immunology. 2002 Mar 28;127(2):156–9.
7. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. European journal of clinical investigation. 2007 Jun 1;37(6):435–53.
8. Cunard R, Kelly CJ. T cell and Minimal Change Disease. Journal of the American Society of Nephrology. 2002 May 1;13(5):1409–11.
9. Eckardt KU, Kasiske BL. KDIGO Clinical Practice Guideline for Glomerulonephritis. Volume 2, issue 2, June 2012.
10. Poliantseva LR, Klepikov PV, Varshavskiĭ VA. Nephrotic syndrome in a patient with systemic mastocytosis. Klinicheskaia meditsina. 1983 Jul;61(7):115–9.
11. Lal SM, Brooks CS, Luger AM, et al. Systemic mastocytosis associated with membranous nephropathy and peripheral neuropathy. American Journal of Kidney Diseases. 1988 Dec 31;12(6):538–43.
12. Diamantidis MD, Myrou AD, Kaiafa GD, et al. Aggressive Systemic Mastocytosis Associated with Mesangioproliferative Glomerulonephritis. Acta haematologica. 2010 Dec 24;125(3):153–9.
13. Holdsworth SR, Summers SA. Role of Mast Cells in Progressive Renal Diseases. Journal of the American Society of Nephrology. 2008 Dec 1;19(12):2254–61.
14. Blank U, Essig M, Scandiuzzi L, et al. Mast cells and inflammatory kidney disease. Immunological reviews. 2007 Jun 1;217(1):79–95.
15. Miyazawa S, Hotta O, Doi N, et al. Role of mast cells in the development of renal fibrosis: Use of mast cell-deficient rats. Kidney international. 2004 Jun 1;65(6):2228–37.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

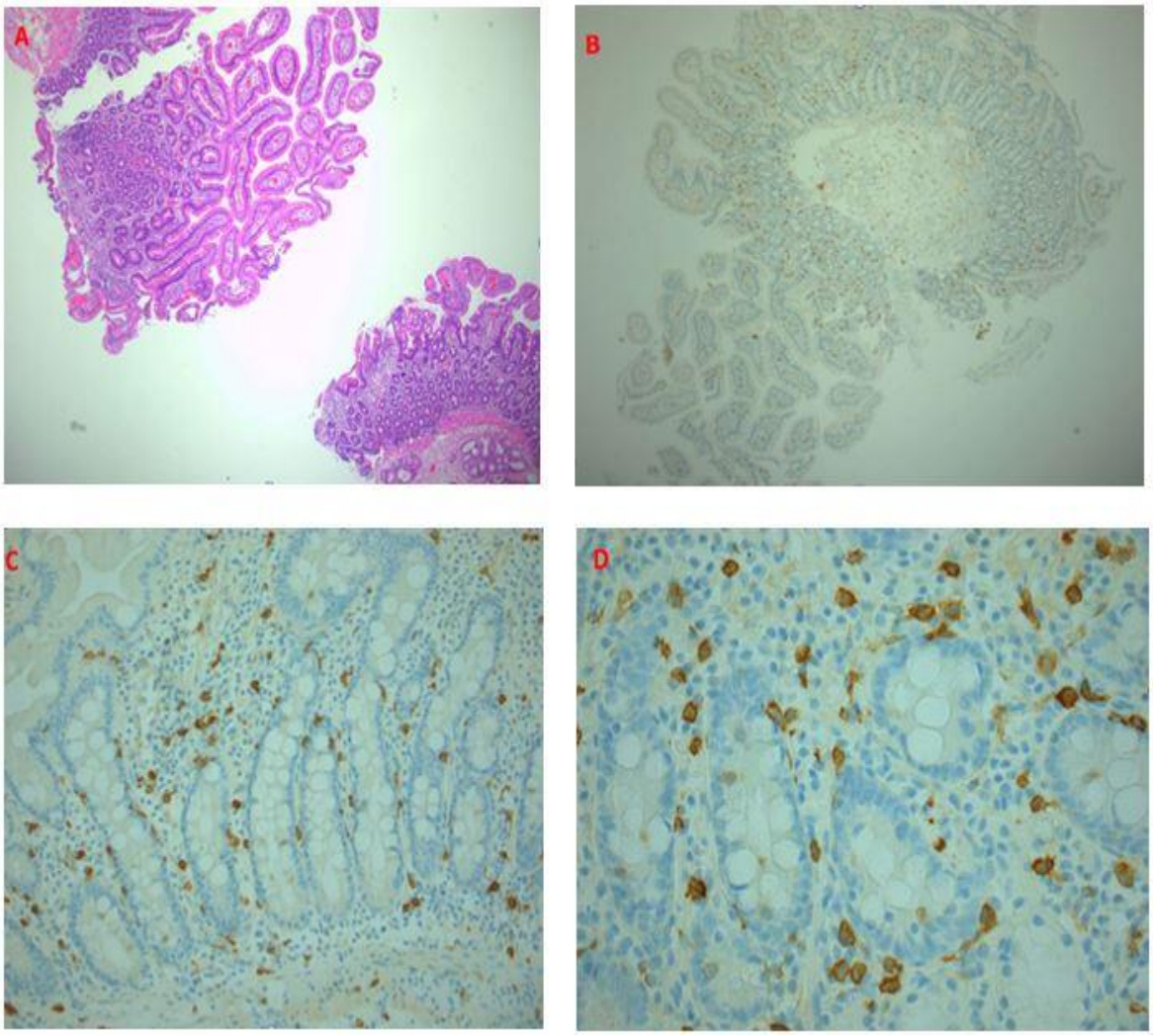
FUNDING

Self-funded

PATIENT CONSENT

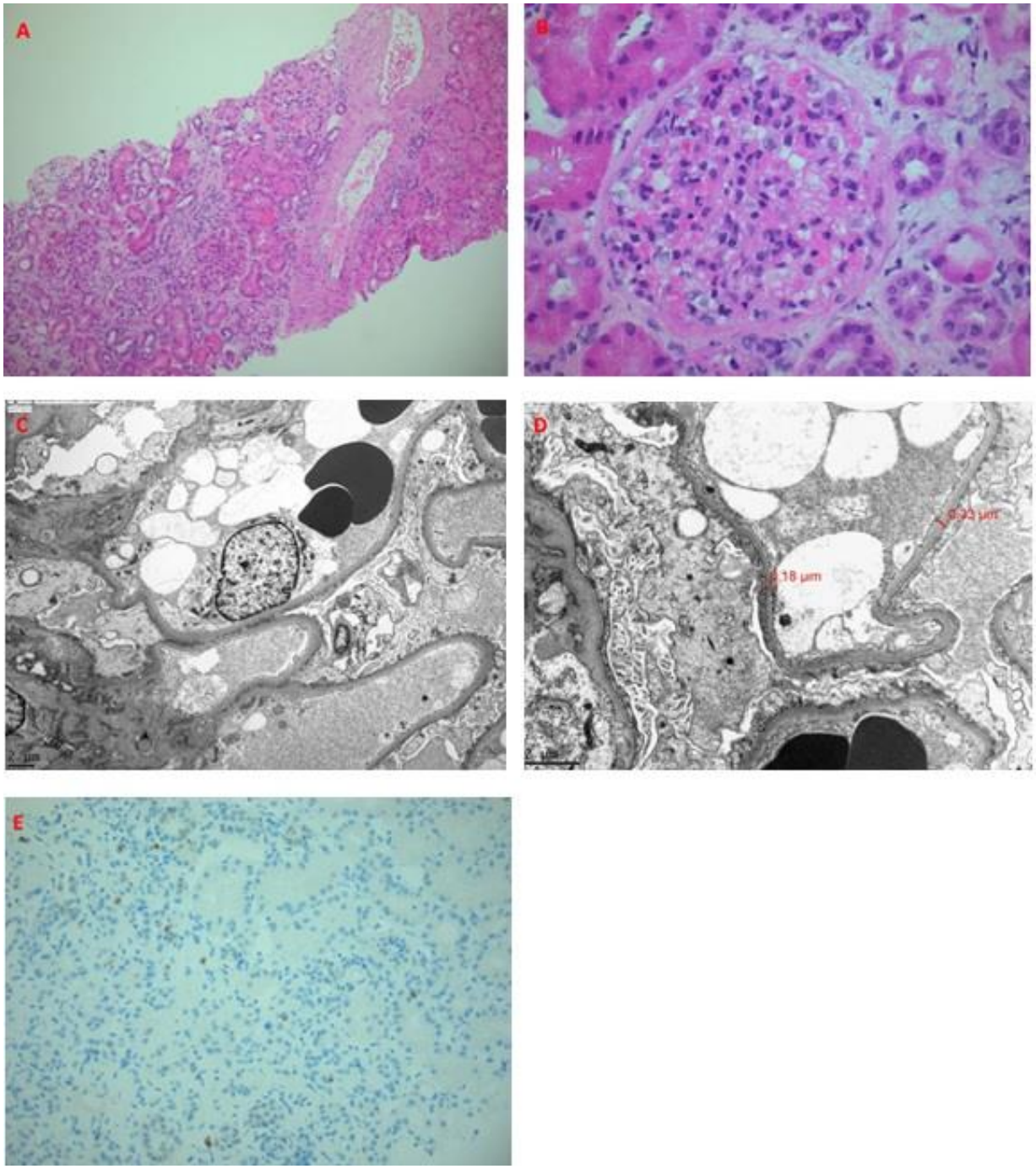
All possible steps have been taken to safeguard the identity of the patient(s).

Figure 1: Duodenal biopsy



A: *Normal long sinuous villi and Brunner's gland in the bottom left corner, confirming the site of biopsy as the duodenum.* ***B, C, D:*** *C-kit staining of the duodenum, highlighting mast cells.*

Figure 2: Renal core tissue



***A** Light microscopy showing mild interstitial fibrosis; **B** Light microscopy showing normal glomerulus; **C, D** Electron microscopy shows diffuse flattening of podocytes; **E** C-kit staining, highlighting mast cells.*