Gastrointestinal tract involvement by systemic disease

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Plan

- Sarcoidosis
- Amyloid
- Mast cell disorders
- IgG4-related disease
- Dermatological conditions
- Behcet’s disease

Sarcoidosis

- Chronic multisystem disorder characterised by multiple granulomas in affected organs
- Wide spectrum of clinical effects
- May be asymptomatic or associated with severe clinical features
- Incidence hard to ascertain and higher in post-mortem studies
- Mainly young adults, F>M, African Americans>Caucasians
- >90% show pulmonary involvement

Liver involvement

- Up to 70% show liver involvement
- Usually asymptomatic
- Portal tract & parenchymal granulomas and scarring may lead to cirrhosis directly or via secondary biliary cirrhosis
- Portal hypertension
- Jaundice due to liver or bile duct involvement or extrinsic compression
- Ascites due to portal hypertension or peritoneal nodules

Granulomas in the liver

- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Autoimmune hepatitis
- Viral hepatitis

Sarcoidosis

GI involvement

- Luminal GI tract involvement relatively rare
- Stomach is most commonly involved site
- Other more common causes for granulomatous gastritis exist
- Oesophagus: uncommon, but the larynx can be involved
- Mucosal involvement commonly asymptomatic
- Extrinsic compression may occur

Sarcoidosis

Diagnosis

- Granulomatous inflammation
- Appropriate clinical context
- Exclusion of alternative granulomatous conditions
- Necrosis not usual but necrotising sarcoidosis can occur
- Serology e.g. angiotensin-converting enzyme, soluble interleukin-2 receptor (Th1 cells), neopterin (macrophages)
Sarcoidosis
Practical points
- Portal tract and parenchymal involvement can lead to cholestasis and portal hypertension
- Mucosal involvement may be seen in the luminal GI tract – often as an incidental finding
- Differential diagnoses include many other granulomatous conditions which need to be excluded e.g. with appropriate additional stains for infective organisms as well as careful clinicopathological correlation

Amyloid
Gi & liver involvement
- Wide spectrum of involvement
- Liver involvement mainly sinusoidal and may be very extensive before biochemical dysfunction occurs
- Luminal GI tract involvement initially in blood vessel walls and then lamina propria e.g. subepithelial
- Symptoms include diarrhoea, steatorrhoea, anorexia, weight loss, nausea/vomiting and dysmotility/pseudo-obstruction

Amyloid Diagnosis
- Demonstration of amyloid in tissues
- Early deposition e.g. within blood vessel walls, advanced disease obvious
- Congo red, IHC – p-component, amyloid A, kappa and lambda
- Molecular assessment of TTR genotype
- Don’t confuse with light chain disease
- Clinicopathological correlation important

Amyloid Practical points
- May be identified incidentally, while GI biopsies sometimes taken to look for amyloid deposition
- Within Gi biopsies, deposition most commonly seen in subepithelial region and within submucosal blood vessels
- Within liver, portal tract blood vessels commonly affected but deposition may be marked within sinusoids
- Congo red characteristic, IHC also useful

Mast cell disorders
- Mastocytosis relates to a range of conditions characterised by the presence of prominent mast cells that are clonal in nature
- Cutaneous or systemic
- Indolent or aggressive
- Most common in children – especially cutaneous
Mast cell disorders

Cutaneous – urticaria pigmentosa associated with erythematous macules, papules and nodules

Systemic – spectrum of associations include a range of leukaemias

Systemic disease may be occult or associated with e.g. pruritus, flushing, tachycardia, asthma, headache, weight loss

Mastocytomas may occur

Histamine and heparin release from mast cells

Classification of mast cell disorders

Cutaneous mastocytosis

Indolent systemic mastocytosis

Systemic mastocytosis with an associated clonal non-mast cell disease

Aggressive systemic mastocytosis

Mast cell leukaemia

Mast cell sarcoma

Extracutaneous mastocytoma

Myelomastocytic leukaemia

Mast cell activation syndrome

Mast cell hyperplasia

GI & liver involvement

50-80% with systemic mastocytosis have GI tract-related symptoms e.g. nausea & vomiting, abdominal pain, diarrhoea, steatorrhoea

Peptic ulceration may occur

Involved mucosa may show villous atrophy, submucosal oedema and variable mast cell infiltration & prominent eosinophils

Mast cells within glands, degranulation

Liver not uncommonly involved – mast cell infiltrates, fibrosis, non-cirrhotic portal hypertension, cholestasis, ascites

Diagnosis

May be difficult, especially in early disease and/or when clinical features mild/non-specific

Raised serum tryptase, eosinophilia, or pancytopenia with marrow involvement/leukaemia

Eosinophil-rich lymphoid aggregates

IHC – CD117, mast cell tryptase, CD25

PCR-based identification of KIT D816V mutation

Eosinophil-rich infiltrates

Urticaria pigmentosa

Systemic mastocytosis

Eosinophilic syndromes e.g. Churg-Strauss syndrome

Allergic conditions e.g. asthma

Eosinophilic gastroenteritis & colitis

Parasitic infections

Hodgkin's disease & T-cell lymphoma

Langerhan's cell histiocytosis

Inflammatory bowel disease

Practical points

Mastocytosis is a wide spectrum of conditions

Mast cells are normal GI lamina propria cells

Diagnosis requires prominent mast cell infiltrates in an appropriate clinicopathological context

Diagnosis should be considered when a monotonous infiltrate of regular lymphoid cells present, often with eosinophils

Mast cells can be difficult to identify on H&E and special stains required

IgG4-related disease

Lymphoplasmacytic chronic inflammation, storiform fibrosis

Common in systemic involvement with an associated chronic inflammatory non-carcinomatous disease

Affects almost any anatomical site

30% have a history of atopy

GI & liver involvement

First recognised as a cause of chronic pancreatitis – type 1 autoimmune pancreatitis

Pancreatic involvement may be focal or diffuse

Hepatobiliary involvement relatively common, leading to IgG4-associated cholangitis with strictures, intrahepatic masses and an autoimmune pattern hepatitis

Luminal GI tract involvement less common, with masses simulating malignancy and possibly polyps

Abscess in a case of sinusitis, orbital inflammation, mast cell hyperplasia, IgG4-related disease

Common in systemic involvement, storiform fibrosis

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Common in systemic involve
**IgG4-related disease**

**Diagnosis**
- Mayo criteria
- Boston criteria for histopathological features
- Classical morphological triad
  - Prominent IgG4+ plasma cells
  - IgG4+/IgG+ ratio >40%
- Exclusion of mimics: adjacent to certain tumours, chronic inflammatory oral conditions, others (e.g., rheumatoid disease)

**Boston triad**
- Lymphoplasmacytic inflammation
- Storiform fibrosis
- Obliterative venulitis

**Practical points**
- May involve one or multiple anatomical sites
- Diagnosis based on clinical, radiological and histopathological factors (published criteria)
- Histopathological assessment involves identification of key morphological criteria, prominent IgG4+ plasma cells and an IgG4+/IgG+ ratio of >40%
- Sampling variability and immunosuppressive treatment may alter histopathological features
- Prominent IgG4+ plasma cells may also be found in other (non-IgG4-related disease) conditions

**Dermatological conditions**

**Examples**
- Coeliac disease and dermatitis herpetiformis
- Inflammatory bowel disease and cutaneous manifestations
- The oesophagus and various skin conditions
- The liver and treatment for skin diseases

**Practical points**
- Many conditions involve both the skin and GI tract
- There is an association between psoriasis and non-alcoholic fatty liver disease
- Treatments for certain skin conditions may affect the GI tract (e.g., psoriasis and methotrexate, acne and vitamin A)
- The above particularly affect the liver and MTX used to be a relatively common indication for liver biopsy
- However, the advent of serum fibrosis markers and elastography has led to reductions in liver biopsy

**Behcet’s disease**

**GI & liver involvement**
- Luminal GI involvement relatively unusual
- Small intestinal ulceration
- Perforation and haemorrhage
- Inflammatory masses with obstruction
- Liver involvement uncommon
Behcet’s disease
Diagnosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Characteristic clinical picture</td>
<td>1</td>
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<tr>
<td>Exclusion of differential diagnoses</td>
<td>1</td>
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<tr>
<td>Sets of criteria e.g. International Study group for Behcet’s Disease (ISG)</td>
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<tr>
<td>GI ulcers usually show non-specific features</td>
<td></td>
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<tr>
<td>Lymphocytic vasculitis – especially veins</td>
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<tr>
<td>Leukocytoclastic vasculitis also described</td>
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<tr>
<td>Histological features may overlap with Crohn’s disease</td>
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Behcet’s disease
Practical points

- Rare condition characterised by the presence of mucosal ulceration and other features e.g. arthritis
- Histological features of GI biopsies often non-specific but characteristic finding is lymphocytic vasculitis affecting submucosal veins
- Diagnosis requires recognition of appropriate clinical features and may be supported by appropriate histological appearances, even if GI biopsies do not show classical pattern of vasculitis

Conclusion

- Many systemic diseases can affect the luminal GI tract and/or the liver
- Wide spectrum of clinical manifestation depending on pattern and extent of involvement
- Involvement may be asymptomatic
- Diagnosis may be incidental or critical and usually relies on clinicopathological correlation
- Treatments for systemic disease may also result in important changes