Macrophages and histiocytes in the Digestive tract

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Histiocytic subpopulations in the GI tract
Schneider e a
Appl Immunohistochem Mol Morph 2004; 12; 356

• Langerhans cells CD1+ squamous mucosa of oesophagus and anus
  — Antigen presentation & cell mediated immunity

• FXIIIa-positive dendritic cells : throughout the GI tract
  — Effector phase of cell and humoral immunity in association with CD68+ cells

• CD68+ macrophages : throughout the GI tract (mucosa and submucosa)
  — Phagocytosis, antigen processing for T cell presentation, cell mediated immunity
  — Non-pigmented
  — Pigmented
    • Endogenous pigment
    • Exogenous pigment
Oesophagus Langerhans cells

Stomach

• Xanthoma - tosis : non pigmented cells
  – aggregates of foamy histiocytes 1 – 2 mm (post surgery – Billroth II)
  – CMV infection \( \text{(Lerut E e a Tijdschr Geneesk 2002; 58: 985)} \)

• Pigmented cells :
  – Metastatic melanoma
  – Other conditions
  \• Drugs : \text{Erosive Injury to the Upper Gastrointestinal Tract in Patients Receiving Iron Medication An Underrecognized Entity AJSP, 23(10):1241-1247, 1999.}
Pigmented macrophages in the stomach

• N = 500 pts with gastric biopsies
• Prussian blue stain + in 3.6%
• Three patterns
  – Extracellular deposition  ORAL INGESTION OF IRON
  – Extracellular deposition with focal stromal and epithelial cells
  – Deposition in antral and fundic glandular epithelium  HEMOCHROMATOSIS
This is a picture of a case of gastric melanosis which was very apparent endoscopically. The brown pigmentation was not caused by iron or by melanin, since both the Perl’s and the Fontanna Masson or melanin stain were negative. Up until now we do not know the cause of this heavily brownish pigmentation. Pigmentation due to a pharmaceutic agent is likely but could not be proven.

Macrophages and colon
(and small intestine)

Macrophages are ubiquitous in the mucosa of the digestive tract but not conspicuous in normal colon
Present in the upper lamina propria
- Underneath surface epithelium
- Underneath superficial capillaries

- Protect mucosa against pathogens and scavenge cellular debris
- Resident macrophages are CD14⁻ and thus anergic (CD14= pattern recognition receptor)
- In infection and inflammation, CD14⁺ cells are recruited from the blood for phagocytosis and release of inflammatory mediators
Normal digestive tract: Macrophages > heterogeneous population

Staining properties
- Special stains
  • PAS positive (weakly)
  • Mucin
- Immunohistochemistry
  • CD68/PG-M1; S100; HLA-DR positive
  • Lysozyme positive
- Enzyme histochemistry
  • Strong or weak acid phosphatase positive
  • Membrane adenosine triphosphatase positivity

2014

Macrophages in the small intestine
Infections

Mycobacterium Avium intracellulare

Ziehl stain

2014
Whipple’s disease
Morphologic approach of the mucosal defence in chronic gastrointestinal inflammatory conditions Ectors, PhD thesis 1994

- Rare disorder
- Annual incidence: less than 1/1 000 000
- Middle aged man – male to female ratio 8/1
- Multisystemic chronic disease caused by Tropheryma whippelii (ubiquitous in the environment – water)
- Healthy individuals can be carriers
- Primary involvement: small intestine
Localised massive tumourous xanthomatosis of the small intestine

- 68-year old male patient
- Localised, massive accumulation of vacuolated, mostly lipid-loaded macrophages
- Infiltrative pattern involving also the muscularis propria
- DD
  - xanthogranulomatous inflammation (no inflammation)
  - (isolated) xanthoma(-tosis) multiple nodules involving also the muscularis propria
- Coletta & Sturgill Hum Pathol 1985; 16: 422
Macrophages and the Colon

• Pigmented

Macrophages and the Colon

• Pink - Foamy macrophages

• Lou e.a. Hum Path 1971; 2; 421
  Colonic histiocytosis : 34/50 (68%) consecutive rectal biopsies : small collections of PAS+ cells

• Bejarano e.a. Am J Surg Pathol 2000; 24; 1009
  40% of biopsies +; associated changes point to healing phase

• In IBD :
  – Increased numbers
  – Significant expression levels of T-cell costimulatory molecules CD40, CD80, CD86, and CD14 and CD89
  – Different from usual anti-inflammatory phenotypic

Smith e.a. Mucosal immunology 2011,4,31-42
Case report
Deraedt K 21 ESP congress Istanbul 2007

• 57-year-old female
• Diarrhoea
• Fever of unknown origin
CD68

PAS
Diastase PAS
Diagnosis

Whipple’s disease
Infection by Tropheryma whippelii

2014
Case: History

66 yr male
• Marked weight loss and occasional nausea
• No other GI symptoms (no abdominal pain, no diarrhea, no GI bleeding)
• Medications: Oxazepam, Gravol, Zopiclone
• Physical
• Emaciated/cachectic (49 kg)
• No organomegaly, lymphadenopathy, masses or edema

• Duodenal biopsy

Duodenal histiocytes

2014
Case: History

- 32-year-old male
- Fatigue, watery diarrhoea, diffuse sweating (after journey to the Philippines)
- Diarrhoea for 5 years
- No melaena
- Stool examination negative
- Ileocolonoscopy: numerous white, smooth mucosal nodules in colon and rectum
Case: Findings

1. Diarrhoea
2. White, smooth nodules in colon & rectum
3. Ileal & colonic biopsies:
   • Foamy macrophages (CD68 +)
   • Oil-red-O +, PAS & diastase PAS faintly +
   • EM: fat droplets in macrophages & smooth muscle cells
4. Blood tests: hyperlipidaemia (↑LDL, ↓HDL and ↓apolipoprotein A1)
Cases: Diagnosis

Suspicious of cholesteryl ester storage disease (CESD)
Further investigation necessary

Cholesteryl ester storage disease

- AR, lysosomal storage disease
- Reduced activity of lysosomal acid lipase
  → intralysosomal storage of cholesteryl esters and triglycerides
  → foamy cells in liver, spleen, intestine, lymph nodes, ...
- Hepatomegaly and early atherosclerosis
Cholesteryl ester storage disease

- CESD and/or Wolman's disease is an autosomal recessive condition with a defect of acid lysosomal lipase (LAL).
- Typical Wolman's disease is usually diagnosed in newborns and often lethal. In CESD LAL activity is decreased while in Wolman's disease it is almost absent.
- Currently more than 50 mutations of the encoding gene (LIPA) have been reported being homozygous or compound heterozygous.
- L336P is a variant which appears to be associated with milder forms of CESD.
- Presentation and clinical course variable
  - We have seen three cases: 22 yrs; 33 yrs and 81 yrs old
  - In the oldest patient, the finding was accidentally during colonoscopy for colorectal cancer

Differential diagnosis of macrophages in the colon

1. Foamy macrophages

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Whipple's disease</th>
<th>Mycobacterium avium</th>
<th>Rhodococcus equi</th>
<th>Pneumocystis carinii</th>
<th>Leishmaniasis</th>
<th>Histoplasmosis</th>
<th>PAS, diastase PAS</th>
<th>Ziehl Grocott</th>
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<tbody>
<tr>
<td>Mucins</td>
<td>Low grade injury</td>
<td>IBD, GVHD</td>
<td>PAS, mucicarmine</td>
<td>alcian blue</td>
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<tr>
<td>Lipids</td>
<td>Xanthelasma</td>
<td>Oil-red-O</td>
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<tr>
<td>Abnormal glycoproteins / glycolipids</td>
<td>Metabolic storage disease (lysosomal storage disease)</td>
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<td>PAS, Oil-red-O Electron microscopy</td>
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</tbody>
</table>
### Mucosal metabolic storage disease

<table>
<thead>
<tr>
<th>Lipid storage diseases</th>
<th>Gaucher’s disease</th>
<th>Niemann-Pick’s disease</th>
<th>Cholesteryl ester storage disease</th>
<th>Wolman’s disease</th>
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<tbody>
<tr>
<td>Glycoproteinoses</td>
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<td>Mucolipidoses</td>
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<td>Mucopolysaccharidases</td>
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<td>Hurler’s disease</td>
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<td>Gangliosidases</td>
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<td>Disorder of lipid metabolism</td>
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<td>Tangier disease</td>
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### Storage disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Macrophages</th>
<th>Endothelial cells</th>
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<tr>
<td>Krabbe disease</td>
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<td>Tay Sach’s disease</td>
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<tr>
<td>Gaucher’s disease</td>
<td>-(+)?</td>
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<td>Fabry’s disease</td>
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<td>+</td>
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<td>Batten’s disease</td>
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<tr>
<td>Niemann Pick (type A, B, C)</td>
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<td>Pompe’s disease</td>
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<td>Tangier’s disease</td>
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<td>Wolman’s disease</td>
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<tr>
<td>Cholesteryl ester storage disease (CESD)</td>
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<td>Mucopolysaccharidoses</td>
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<td>Cystinosis</td>
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Niemann Pick

Uncommon conditions
Cristal storing Histiocytosis
Accumulation of Charcot Leyden cristals in eosinophilic colitis (Lewis ea Am J Surg pathol 2007; 31, 481)

TEM showing needle shaped cristals

A) Highly eosinophilic needle shaped crystals
B) CD68 stain
• CVID : n = 43
• X-linked agammaglobulinemia (X-LAG) : n = 23
• Pathology
  – Acute GVHD : stomach (n=4) small intestine (n=3) colon (n=3)
  – Villous atrophy : n = 3 CVID
  – Giardia : n = 3 CVID
  – Lymphoma small intestine : n = 2 CVID
  – Collection of histiocytes containing cellular debris in small bowel : n = 1 CVID
Conclusion

1. Collections of foamy macrophages are a common finding in mucosal biopsies of the colon but rare in the small intestine — Isolated (invisible on H&E) ↔ Aggregated

2. Submucosal macrophages are rare — in the small intestine the presence is usually significant

3. Mostly muciphages & clinically unimportant, remnant of mucosal damage


Differential diagnosis

• Lipid islands (Remmele e a Path Res Pract 1988; 183: 336) also called Lipid proctitis (Romeu & Rybak N Engl J Med 1979; 301: 1099
Differential diagnosis of macrophages in the colon

2. Pigmented macrophages

<table>
<thead>
<tr>
<th>Lipofuscin</th>
<th>Melanosis coli</th>
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<tr>
<td>Melanin</td>
<td>Increased apoptosis</td>
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<td>Metastatic melanoma</td>
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<td>PAS +, melanin –</td>
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<tr>
<th>Haemosiderin</th>
<th>Prior mucosal haemorrhage</th>
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<tr>
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<td>Haemosiderosis</td>
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<td>Mucosal prolapse</td>
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<td>Endometriosis</td>
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<td>Iron +</td>
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<th>Schistosomiasis</th>
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<th>Atmospheric dust</th>
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(Pseudo-)Melanosis coli

Morphological and functional changes induced by laxatives in the intestinal mucosa PhD Thesis Carl Spiessens 1991

- Pseudomelanosis – Pseudolipofuscinosis – Colitis pigmentosa
  - History:
    - brownish coloration of colonic mucosa was first noted by Bellard (1825) and described by Cruveilhier (1829)
    - Virchow introduced the name “melanosis”
    - Linked with laxatives, cholagoga and weight-reducing products
  - Incidence: 0.04% - 59.5%
Pseudomelanosis coli

**Distribution**

- Limited to the colon starting abruptly at the ileocaecal valve
- Spreads over entire colon starting from the caecum, reaching the rectum only in severe cases
- Starts within one year after the start of consumption of the drug
- Disappears six to eleven months after stopping the drug
- Mucosal distribution
- Associated with plasma cells, mast cells and eosinophils
- Not in neoplastic tissue
Pseudomelanosis coli

- **Adverse effects**
  - Moderate influence on epithelial cell proliferation, cancer risk?

- **Origin of pigment**
  - Interaction with mature surface epithelial cells (apoptosis)
  - Cellular debris are ingested by macrophages

---

Recovery of metabolites from tissue
Athmospheric/food additives dust

- Particularly in macrophages associated with Peyer’s patches (situated in the base) in the small intestine
- In stroma
- Appearance: dark brown or black (pigment rich in aluminium, silicon and titanium)
- Frequency 34/42 (over 6 yrs of age) (Shepherd e a Hum Pathol 1987; 18: 50)
- Sampling through M cells
- Powell e.a. Gut 1996; 38: 390

Ileum – Deposition of iron
Case report 1

- Female patient, ° 1982, † 2013
- Chronic diarrhea, Weight loss, Malabsorption
- Repeated small intestinal biopsies
  - Mild villous atrophy, Epithelial lymphocytosis (25-30/100 epithelial cells)
- Serology for coeliac disease
- No response with gluten free diet
Case report 2

- Male patient, age 65
- First hospitalization: age 38 for right lower quadrant pain
  - Surgical treatment: pericaecal mass; diagnosis > Crohn’s disease
- Two years later: fistulisation > right hemicolectomy
  - 25 year follow up: unremarkable
  - Reoperation because of recurrent episodes of subobstruction
Brown Bowel Syndrome

Brown pigment in smooth muscle (and surrounding macrophages)  
First described in 1861

Pigment: lipofuscin  
To differentiate from haemosiderin  
  Perls negative  
  Schmorl's ferric ferricyanide: blue  
  PAS - PAS diastase: red  
Smooth muscle mitochondrial myopathy  
Secondary to malabsorption  
  Especially lack of vitamin E  

Case 1: Malabsorption due to lysosomal storage disorder (submucosal macrophages = PAS negative)  
Case 2: Malabsorption secondary to inadequately treated Crohn's disease
Macrophages in (primary) immune deficiencies in pediatrics

- Chronic granulomatous disease: recurrent infections due to a defect in the phagocytes (NAPDH oxidase activity and generation of oxygen species)
  - Lipid-laden histiocytes in the deep lamina propria of the colon (can be vaguely brownish pigmented)
- Hermansky-Pudlak syndrome and glycogenosis type IB
  - Ceroid pigment
- Severe Combined immunodeficiency (subtype Cartilage hair hypoplasia)
  - Brownish pigment
Macrophages in (primary) immune deficiencies in pediatrics

1496651 Cartilage Hair Hypoplasia A. Duodenum: villous blunting with degenerative changes of the intestinal epithelium and brown-pigmented histiocytes in the lamina propra (OM: x200) - Finely granular brown pigment in the histiocytes (OM: x400)

Differential Diagnosis
Mastocytosis

Nodularity in the colon

Kirsch, Geboes e a Mod Pathol 2008; 21: 1508
Winnepeninckx 18 ESP congress Berlin 2001

2014
Mast cell granules (Giemsa) Immunohistochemistry (tryptase – CD117) TEM

Waldenström’s Macroglobulinemia
Waldenström’s Macroglobulinemia
Staining for kappa light chain

Pneumatosis coli

Major Systemic conditions associated with
- Chronic pulmonary disease
- Chronic heart disease
- Scleroderma
- Leukemia

GI conditions associated with
- Pyloric stenosis
- Cholelithiasis
Conclusions

• Macrophages are ubiquitous
• They form a heterogeneous population
• Small collections in the colon are usually indicators of (previous) damage
• Atmospheric dust in the distal ileum (Peyer’s patches) is not uncommon
• Larger accumulations must orient towards pathology
  – Accumulation of exogenous pigment
  – Accumulation of endogenous pigment
  – Storage disorders

References

5. Byers RJ, Marsh P, Parkinson D, Haboubi N.Y. Melanosis coli is associated with an increase in colonic epithelial apoptosis and not with laxative use. Histopathology 1997; 30; 160-164.