

Drug-induced gastrointestinal injury (DIGI). Updates, reflections and key points

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Key words

Drug-induced gastrointestinal injury • Identifiable drugs • Angiotensin receptor inhibitors • Immuno-modulators

Summary

The goals of this short narrative review are 1) to provide an update in recent developments in the field of drug-induced gastrointestinal injury (DIGI), and 2) to distill few key points to approach with confidence a difficult and vast area of gastrointestinal pathology. DIGI is a challenging diagnosis as it can produce almost any pattern of the injury of the gastrointestinal tract. The recognition of a pattern and the knowledge of which drugs can produce that pattern, are the first step of the diagnostic process; communication with the clinical

team and a high level of suspicion are then paramount. The pathologist can be the leading clinicians of the care team in few situations in which she/he can recognize the drug at the microscope. Knowledge of the most relevant differential diagnoses of DIGI is essential to avoid significant pitfalls. Finally, several DIGIs due to recently developed immunomodulators used in oncology have shown relevance given their sometimes fatal outcome and the accumulating evidence of a common morphological appearance among them.

Abbreviations

In alphabetical order:

AFB: acid fast bacilli stain; **ARB**: angiotensin receptor blocker; **BAS**: bile acid sequestrants; **CMV**: cytomegalovirus; **CRF**: chronic renal failure; **DDC**: dilated damaged crypt; **DIGI**: drug-induced gastrointestinal injury; **GI**: gastrointestinal tract; **IBD**: inflammatory Bowel Disease; **I-C**: inhibitor of CTLA-4 receptor; **IELs**: intraepithelial lymphocytes; **GVHD**: graft versus host disease; **LC**: lanthanum carbonate; **NSAID's**: non-steroidal anti-inflammatory drugs; **PI**: PD1 receptor inhibitor; **PI3K**: phosphatidylinositol-3-kinase; **SPS**: sodium polystyrene Sulphonate (Kayexalate®)

Introduction

Drugs are known noxae with significant aggressive impact in the gastrointestinal tract (GI). Bates et al. ¹ showed that the overall rate of adverse GI drug effects is 6.5 per 100 hospital admissions. Iatrogenic effects on the GI outside of conditions requiring hospital's care remain unknown and are probably unknowable. To add, it is significant that doctors may not be aware of the existence, quality and/or severity of drug-induced GI injury (DIGI).

Excellent reviews of DIGI are published almost yearly ²⁻⁴. This short narrative review intends not only to provide a comprehensive update on those previous works

(to which we suggest strongly to refer to and upon which we build this update) but also, and above all, to crystallize in key points what we have learnt about DIGI along the years. The goal is to help the practicing pathologist to diagnose DIGI or, at least, to introduce DIGI in a meaningful differential diagnosis.

The basic knowledge

The interaction of drugs with intestine depends mainly on the drug's physical-chemical characteristics, dosage, administration route, size of the pill, formulation (e.g.

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sustained release) and on the recipient variables (e.g. other drugs that may interact, how the drug is ingested, the motility of the intestine, anatomic features, associated diseases). DIGI can be highly specific but more commonly it is not, thus requiring communications with clinical teams and temporal correlation with drug intake or drug stoppage to allow for diagnosis. Diverse controversial clinical situations can appear. On one hand, the intestine can respond to noxae with a very limited repertoire of histological responses/patterns (morphological “funneling”), i.e., various diseases or conditions may overlap in their histological manifestations. On the other, the opposite is also true, that is, one DIGI or one disease can “blossom” into multiple different histological patterns. When should the pathologist consider DIGI? Is DIGI frequent absence of diagnostic specificity a nihilistic sinkhole for the morphologist? In brief the answer is no. In general DIGI should be considered when an increase in eosinophils, in apoptotic activity, in intraepithelial lymphocytes (IELs) does appear, or when vacuolation of cytoplasm is noted in the mucosa cells⁵. We learned also that DIGI should be considered when: multiple portions of the GI are affected by various injury types (e.g. collagenous colitis and increased IELs in stomach), microscopic findings do not fit neatly into a known disease (e.g. apoptotic bodies that are markedly increased in what appears to be Inflammatory Bowel Disease, (IBD)), the clinical context is unusual [e.g. ischemic colitis in a young patient or ischemic gastritis), the patient is unresponsive to what appears to be an appropriate treatment (e.g. gluten free-diet in celiac disease). Nowadays it is fashionable to try to work up the differential diagnosis of gastrointestinal medical diseases using morphological patterns of injury; DIGI, however, escapes this approach as it is not a single disease and it can generate almost any type of injury pattern. The clinical background of the patient is essential not only because the clinician, hopefully, knows the drugs taken by the patient but also because knowing what conditions affect the patient may heighten the pathologist awareness of a DIGI. Certain conditions are treated with drugs that are well known to cause DIGI. A list of such diseases is in Table I.

KEY POINT #1:

DIGI is most often non-specific histologically and can manifest with almost any pattern of injury. Clinical data, awareness and knowledge of DIGI pathology can help in the diagnosis.

It cannot be overemphasized that the nonspecific drug-induced changes are also clinically significant: an example is the impact of apoptotic bodies due to drugs in the diagnosis of Graft Versus Host Disease (GVHD); less than 6 apoptotic bodies/10 crypts post bone marrow transplant (BMT) in the colon are not sufficient for the diagnosis of GVHD since several cases resolve without therapy⁶. Drugs are the most likely cause of this low-grade apoptosis⁶. The diagnosis of “indeterminate for GVHD” post BMT is therefore due to overlap with a nonspecific histological DIGI.

Tab. I. Clinical conditions that should alert the pathologist of drug-induced injury.

Condition	Drugs used affecting GI
Chronic renal failure	Sodium polystyrene Sulphonate, Sevelamer, Lanthanum carbonate
Autoimmune disorders (e.g. lupus, myasthenia gravis, psoriasis) Solid organ transplant	Mycophenolate
Cancer patients (CLL, FL, Melanoma, breast esophagus lung ovary cancer etc)	Taxanes, PDL-1 inhibitors, CCTLA inhibitors, Adalalisib,
Polypharmacy, especially if in elderly or neurologically impaired patients	NSAIDs, Doxycycline, Clindamycin, Bisphosphonates
Hypertension	Angiotensin Receptor Blockers (Olmesartan, Valsartan, Telmersartan)

A more common situation is that of a nonspecific GI ulcer. Drugs are considered the main causes of ulcerations of unclear origin routinely encountered in the GI. Ulcers due to drugs are in the overwhelming number of cases histologically nonspecific. Pill fragments are the most direct evidence of ulcer being a DIGI but this event is rare. Too numerous are the drugs capable of causing erosion/ulcer to be listed here, we provide instead clues for the differential diagnosis. Location of the erosion/ulcer can help. Esophageal “hang-up” areas (such as the aortic arch, the imprinting due to an enlarged left atrium, the gastroesophageal junction) lead to prolonged contact of the drug with subsequent chemical burn. Proximal esophagitis/ulcer is almost always pathognomonic of drug-induced esophagitis (lichen planus is the main differential diagnosis in these cases). The isolated proximal location effectively eliminates gastro-esophageal reflux disease as a cause. In addition to antrum and duodenal bulb, the right colon, and terminal ileum are locations for Non-Steroidal Anti-inflammatory Drug (NSAIDs) ulcers. In case of NSAIDs-induced diaphragms formation the ulcer would typically involve the tips of the diaphragms⁷ (Fig. 1).

Histology can provide some help: NSAIDs-induced ulcer is generally inflammation-poor, superficial, rarely involving the muscularis propria. Tetracyclines notorious esophago-gastro-toxic antibiotics include doxycycline: this antibiotic has gained possible morphological relevance. Doxycycline can cause erosions/ulcers in the entire upper GI but, uniquely so far, doxycycline can cause capillary vascular degeneration with a peculiar “necrotic” appearance and microthrombi⁸ (Fig. 2). In addition, as first described in the esophagus by Medlicott and Dupré⁹, doxycycline causes a lymphocytic vasculitis with endotheliitis and peculiar perivascular pallor due to edema and fibroblast proliferation (Fig. 3). Such pattern should promote an inquiry into doxycycline intake.

As previously stated drugs can induce all the pattern of

Fig. 1. The tip of a NSAID's-induced diaphragm in the small intestine shows typically an ulcer with rolled-in edges, scant inflammation and a nodular group of smooth muscle below.

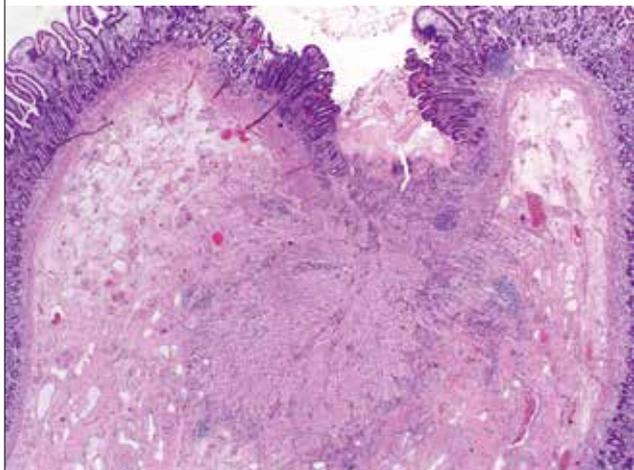


Fig. 2. Necrosis of capillaries (arrows) in gastric mucosa due to doxycycline (from G De Petris et al Int J Surg Pathol 2014; 3:202-11).

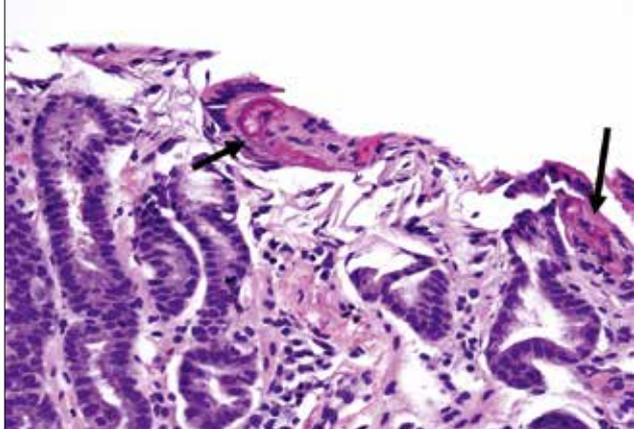
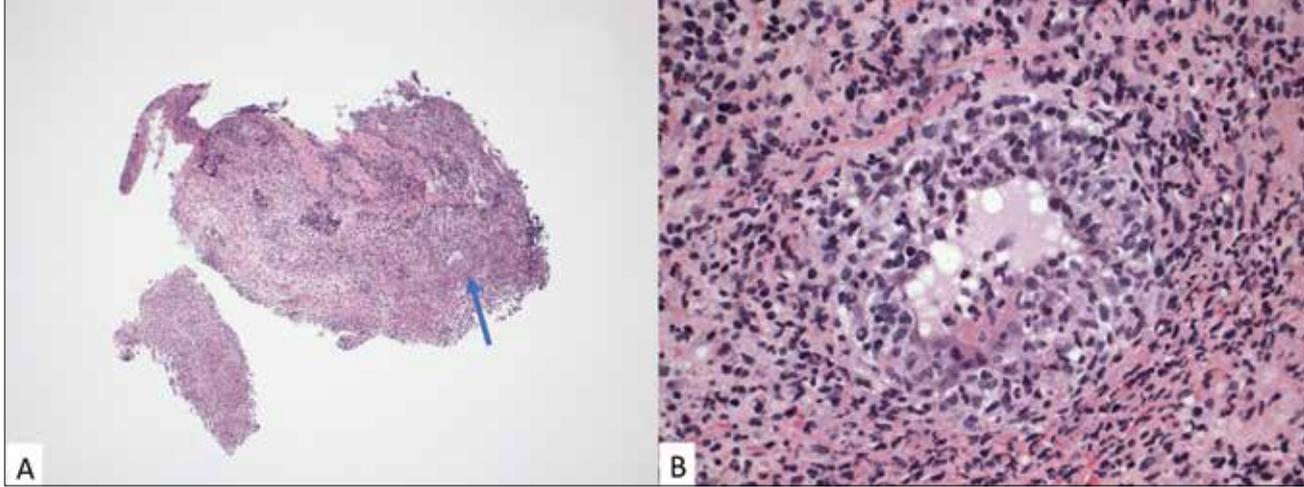


Fig. 3. Doxycycline vascular injury in esophageal ulcer bed. A shows a low power view of the ulcer bed with pallor around vessels. In B the area indicated by the arrow is seen at higher magnification (to highlight the lymphocytic vasculitis (both photos of H-E stained slides). Courtesy of Dr. M Dupre', Dept of Pathology, University of Manitoba, Winnipeg, Canada.



injuries of the GI. Table III is an extensive list of offending drugs and related injury patterns in the various GI organs. Examples have been and will be highlighted in this short review but we defer to previous reviews on the topic for a more exhaustive discussion²⁻⁴.

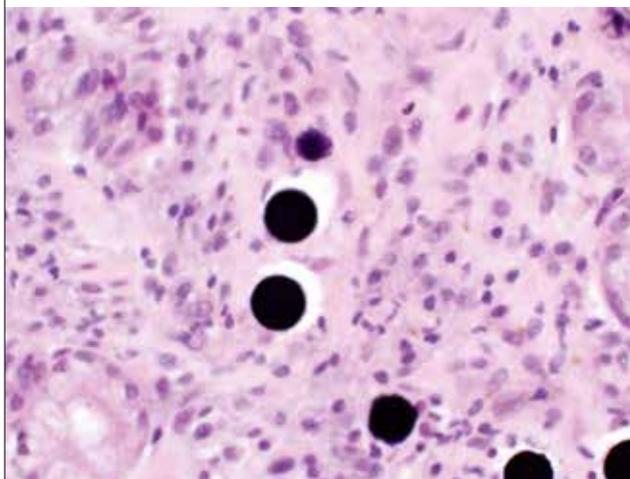
When the pathologist is decisive: "GI mineralogy"

Trained pathologists can astonish clinicians figuring out the patient intake of specific drugs relating them with several GI pathologies that can otherwise appear puzzling or unclear. Certain drugs can manifest as concretions, crystals or amorphous deposits in the GI (Tab. II). Unmistakable are the small and black 30 microns in diameter, round spheres loaded with yttrium-90 (Fig. 4) that are injected in the hepatic artery for internal radiation therapy directed at liver metastasis or hepatocellular carcinoma. An unfortunate diversion of these microspheres (for anatomical or procedural reason) displaces them in the upper GI organs or pancreas. Biopsies of the upper GI can easily detect them.

Pathologists will certainly not miss iron pills residues in the upper GI biopsies. Iron supplements (usually ferrous sulphate) at therapeutic doses can cause symptoms and DIGI in the upper GI in up to 16% of iron deficiency anemia patients¹⁰. Iron deposits due to iron supplements are composed of layers of Perl's stain-positive, fibrillary, yellow/brown to blue/black material on the mucosal surface and in the mucosa. Giant cells and, of course, hemosiderin-laden macrophages may be seen. Of note iron distribution in the stroma and in stromal histiocytes, or in glands, is not iron supplement-related, but follows previous ulcer or is due to hemochromatosis respectively¹¹. DIGI due to iron is almost exclusively in stomach and esophagus and is

Tab. II. Identifiable drug-related material in the GI tract . Calcinosis is entered as it is in the differential diagnosis.

	SPS	Sevelamer	BAS	Iron	OsmoPrep	Lanthanum carbonate	Gastric calcinosis
Location	Mainly colon and upper GIT Luminal, mural, extramural	Mainly colon and upper GIT: Luminal, mural, extramural.	Mainly colon and upper GIT: Luminal.	Stomach: Luminal, lamina propria Duodenum: Histiocytes	Stomach: Luminal and superficial lamina propria	Stomach, colon: histiocytes in lamina propria. luminal	Stomach: lamina propria
Color (H-E)	Purple	Two-toned pink/yellow to deeply eosinophilic rusty brown	Bright orange to black	Yellow/brown to blue black if abundant	Purple/black or translucent	Reddish brownish	Gray brownish
Shape	Angulated irregular square	Irregular square	Angulated squares/shards but can be round	Fibrillary tangles	Concretion	Granules with coral or coiled shapes	Concretion
Appearance	Regular fish scales, narrow curvilinear (can be absent)	Regular fish scales broad or narrow or curvilinear	Homogeneous (rarely with fish scales)	None	None	None	None
AFB stain	Black/dark gray	Magenta	Pale yellow gray, translucent	Negative	Negative	Negative	Negative
Alizarin red	Negative	Negative	Negative	Negative	Negative	Negative	Positive
Von Kossa	Negative	Negative	Negative	Negative	Positive	Can be positive	Positive

Fig. 4. Unmistakable round, black yttrium-90 loaded particles lodged in gastric mucosa (approx. 30 micron in size).

itself erosive producing epithelial reparative changes. Erosions due to iron pills are instead very rare in the duodenum, where iron is seen in the reticuloendothelial cells in tips of villi. In the duodenum iron in lamina propria indicates therapeutic overload¹⁰.

Non-systemic/non-absorbable drugs exert their effects only in the lumen of the GI and are the logical target of microscopic recognition. Among this class of drugs are sequestering agents that act by forming complexes with a target molecule that can then be eliminated in the feces. The recognition of the crystals of these drugs is

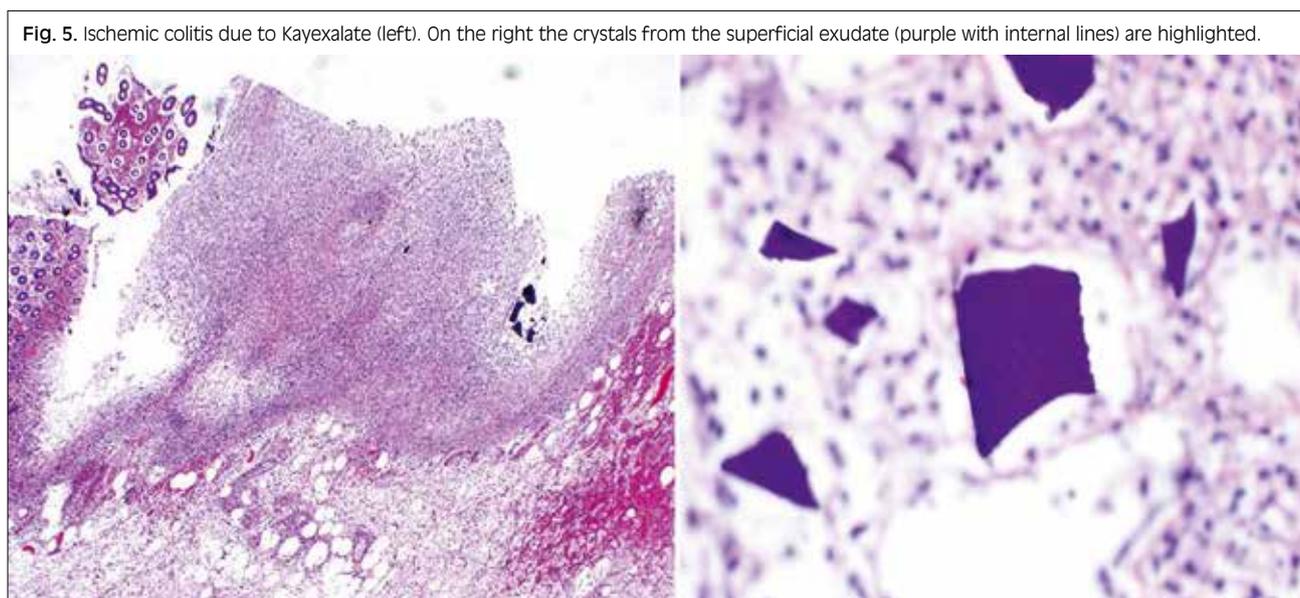
important as some of them can cause death or serious complications.

The best known offending agent among them is Sodium Polystyrene Sulphonate (SPS) (Kayexalate®), a cation-exchange resin used to treat hyperkalemia in chronic renal failure (CRF) patients. SPS, in the market for over 50 years, cannot be used chronically. SPS is administered suspended in sorbitol to prevent bezoar formation, via enema or per os or via nasogastric tube. Side effects occur regardless of the administration route.

Crystals of SPS can be recognized in intestinal biopsies (Tab. II, Figs. 5, 6): they have a square to irregular outline, can vary from 10 to 200 microns or more in size, have a monotonous violet color on hematoxylin-eosin (H-E) stain, and contain regularly spaced “fish scales”-like lines. The best known SPS-side effect is acute ischemic ileitis and colitis in CRF patients¹² (Fig. 5a). Initially sorbitol was thought to be responsible for all SPS-associated DIGI, however when SPS was used alone the risk of severe colonic ischemic injury was not eliminated. It remains advisable to use aqueous (not sorbitol) solutions of SPS. Crystals of SPS can be seen in the exudate or in the intestinal wall or even outside the organ (free or in inflammatory pseudotumors) if perforation has occurred. SPS injuries of the upper GI are either erosions or ulcers^{13 14} or other related diseases, i.e., emphysematous gastritis (see Fig. 6 for SPS associated with a rare case of esophageal pseudo-diverticulosis). SPS-related deaths have been seen almost exclusively after ileocolonic injury^{13 14}. New products are joining the market that can be used chronically (e.g. patiromer) and may have less risks for the patients.

Tab. III. Offending drugs and related lesion patterns in various organs of the GIT.

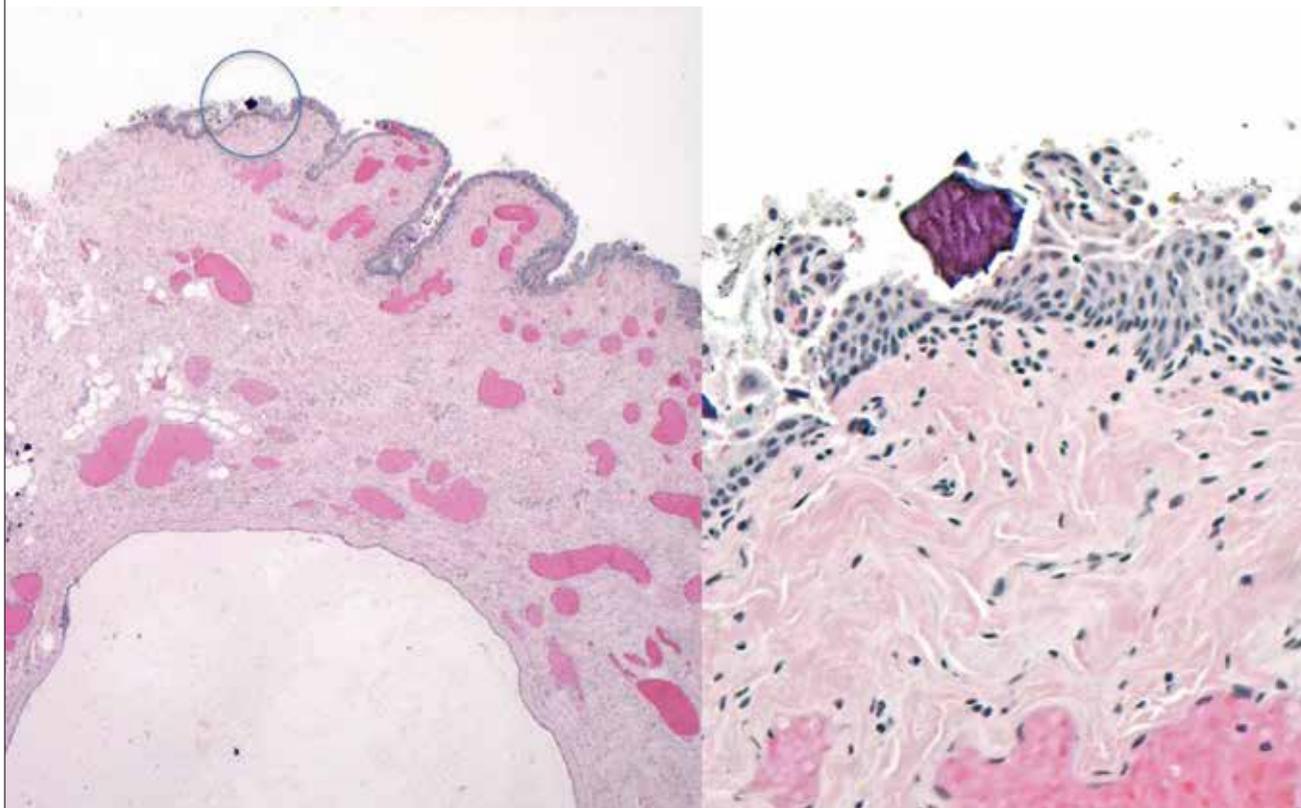
Esophagus	
Lichenoid pattern	Known event but specific drugs studies absent (antimalarial, gold, NSAIDs Thiazides, dental amalgam associated with it)
Eosinophilic pattern	Known event but specific drugs studies absent
Dysplasia-like changes	Taxanes, colchicine
Drug deposits/crystals	Crospovidone, cellulose, iron, SPS, sevelamer, BAS, OsmoPrep
Acute esophagitis	Tetracyclines, bisphosphonates, vitamin C, clindamycin etc (>100 drugs have been involved)
Stomach	
Ischemic	Oxygen peroxide, resins (SPS, sevelamer)
reactive gastropathy	NSAIDs, OsmoPrep, resins, iron, mycophenolate and many more
Collagenous and lymphocytic	Olmесartan
Acute gastritis	Resins (SPS, sevelamer)
Drugs deposits/crystals	Resins, OsmoPrep, Iron, crospovidone microcrystalline cellulose
Infiltrative cellular process	Lanthanum carbonate, clofazimine
Dysplasia-like changes	Taxanes
Granulomatous	Lanthanum carbonate
Small intestine	
Collagenous and atrophic	Olmесartan, methotrexate, NSAIDs, mycophenolate, azathioprine
Lymphocytic	Olmесartan, PPIs, NDSAIDs, PDL-1 inhibitors, CTCLA inhibitors, PI-3-K inhibitors
Infiltrative	Clofazimine
Erosion /strictures/ulcers	NSAIDs
Colon	
IBD-like	Mycophenolate, ipilimumab, rituximab, TNF α inhibitors, NSAIDs, Idelalisib,
Ischemic	Digitalis, estrogens, cocaine, ergotamine, Kayexalate, sevelamer, Glutaraldehyde NSAIDs, PD1 inhibitors
Focal active and self-limited colitis	NSAIDs, sodium phosphate, mycophenolate, ipilimumab
Lymphocytic and collagenous colitis	PPI inhibitors, ticlopidine, NSAIDs, Statins, Idelalisib and many others
Dysplasia-like	Taxanes, colchicine, cyclosporine



Sevelamer carbonate (Rengela[®], Renagel[®]) is a resin targeting phosphate ions used in the treatment of hyperphosphatemia of CRF or tumor lysis syndrome patients. Sevelamer causes chronic diarrhea and constipation. DIGI associated with sevelamer are reported in the up-

per GI (gastric pneumatosis, esophageal ulceration) and, especially, in the lower GI (colitis with crypt distortion and Paneth cell metaplasia, inflammatory polyps, rectocolonic ulcers, colonic stricture, colonic inflammatory mass formation and ischemia, colonic perforation of di-

Fig. 6. An unusual association in the upper GI: esophageal pseudo-diverticulosis, with the superficial kayexalate crystal (in the circle) magnified in picture on the right.



verticulum)¹⁵⁻²⁰, although direct causation is not demonstrated. The features of the luminal crystals are shown in Table II and Figure 7. They are scaly in appearance with the crystal displaying a 2 toned-color appearance: pink and yellow (but also occasionally brown/red/purple). They stain magenta after Acid Fast Bacilli stain (AFB). SPS and sevelamer crystals identification will require a callback to the clinician. However, one must first exclude mimickers: the best known are other resins such as the bile acid sequestrants (BAS) (cholestyramine, colestevam, cholestipol) crystals. BAS have been innocuous so far and their importance lies in their distinction from the ion-binder resins described above. Table II and Figures 5 to 7 provide the clues necessary for identification.

Lanthanum carbonate (LC) is a phosphate binder, devoid of aluminum and calcium, effective in the control of hyperphosphatemia in patients with CRF. No serious side effects have so far been linked to the use of LC. Makino et al.²¹ described LC deposition in gastric mucosa in CRF in 2015. LC deposition is frequent (seen in 14 of 19 CRF patients according to Goto²²) mainly in the stomach but also in duodenum²³ and colon²².

LC has interesting characteristics: 1) is one of the few drugs causing an infiltrative cellular pattern of injury in the GI (another is clofazimine, a third tier anti-tuberculosis antibiotic); 2) it is radio-opaque and detectable using radiological imaging²⁴ while displaying white/chalky granules or polyps at endoscopy with erosions

and ulcers. LC is found in the lamina propria but also on the mucosal surface. The histology is that of a foreign body reaction characterized by an infiltrate of eosinophilic, large, often multinucleated, histiocytes containing colorless or brownish needle-like or branched, coiled or crescent-shaped inclusion bodies (Fig. 8). Formation of well-defined epithelioid granulomas (Fig. 8) is occasionally seen, highlighting again how a DIGI can mimic other conditions, in this case granulomatous gastritis. Regional lymph nodes have similar LC infiltrates²⁴.

The differential diagnosis of crystals/concretions/ crystalline deposits in the GI has been enriched recently by additional compounds: crosopvidone, microcrystalline cellulose and sodium phosphate oral tablets (OsomoPrep[®]) creating a veritable “GI mineralogy” for the pathologist. Crosopvidone (Fig. 9) and microcrystalline cellulose (Fig. 10) are not active principles: they are widely utilized drugs stabilizers and fillers that, when in oral medications, can be recognized in the GI, especially in the small intestine (in 9% of patients according to Shaddy et al.²⁵).

Crosopvidone ranges from 0.4 to 1.5 mm in size, has a coral shape, generally with pink cores and purple coats in each segment on H-E (Fig. 9). It is not birefringent under polarized light and is dark orange after von Kossa stain. Microcrystalline cellulose is instead brightly birefringent under polarized light, and is transparent in H-E-stained slides (Fig. 10). These two compounds are well known to pulmonary pathologists as their presence in

Fig. 7. A collection of crystals of non-absorbable resins as seen in biopsies of the GI. From left to right: (A) Kayexalate (Sodium Polystyrene Sulphonate), (B) Cholestyramine, (C) Sevelamer, and (D) another Bile Acid Sequestrant (BAS), Colesevelam on the far right. Notice how Cholestyramine and Colesevelam, both BAS, are indistinguishable. The colors of Kayexalate and Sevelamer are distinctive and diagnostic in the majority (but not all) cases. From G. De Petris et al. *Int J Surg Pathol.* 2014; 2:120-8.

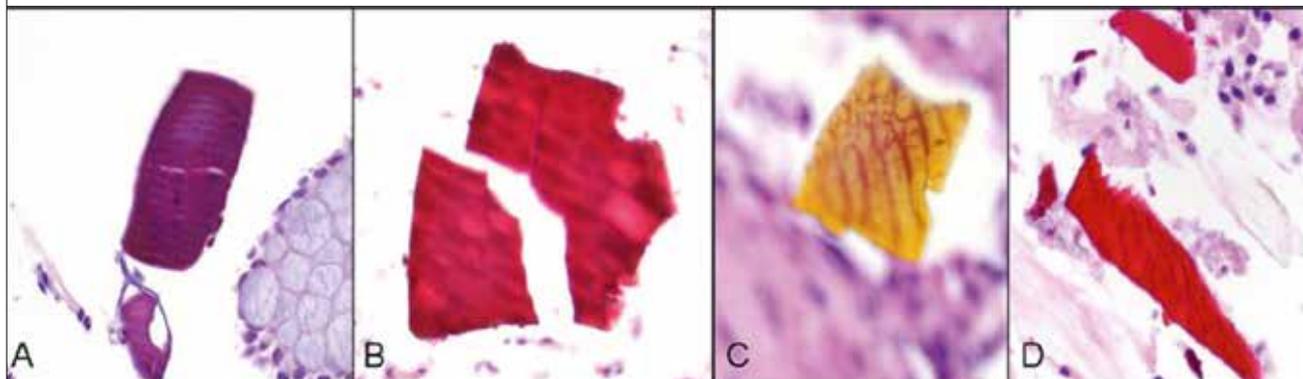


Fig. 8. Lanthanum carbonate (LC) deposits in histiocytes in gastric lamina propria (A), higher magnification of histiocyte with crystals of LC in B. The lamina propria may contain well-formed granulomas (C) (notice histiocytes with LC inclusion below the granuloma). Figure 8A and 8B courtesy of Dr. M Makino Shinonoi-Ai, Nagano, Japan.

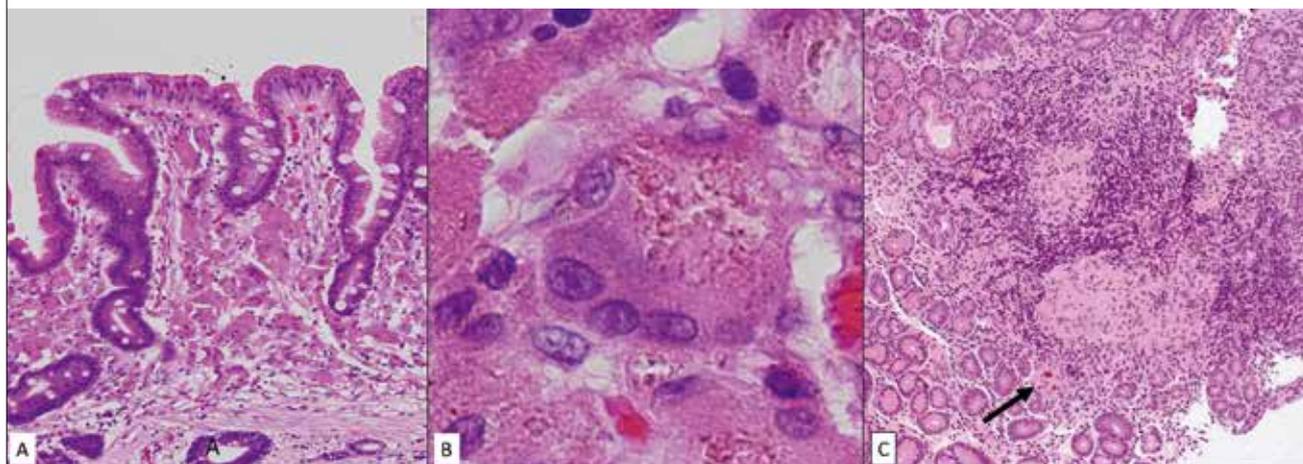
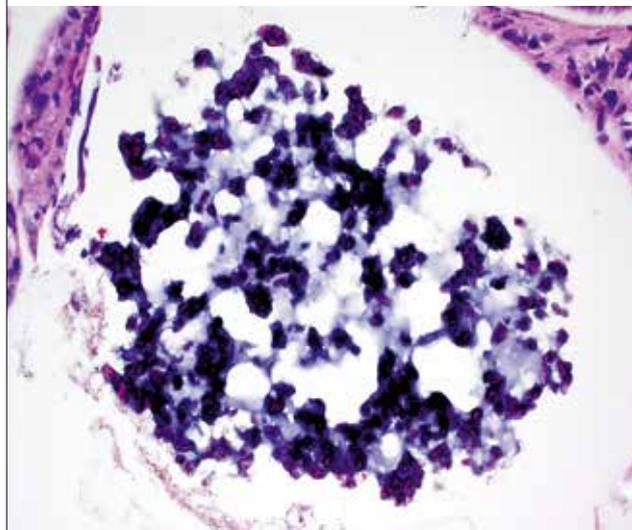


Fig. 9. Crospovidone (H-E stained slide, 40X magnification). Note the pink cores and purple coats in the tangles of the coral-like structure of crospovidone. Courtesy of Dr. R. Gonzales Univ. of Rochester, Rochester NY, USA).



the lung indicates aspiration or intravenous drug abuse. The appearance in the lungs and GI is however different: while in the lung crospovidone is solid blue or black on H-E-stained sections, in the GI has a two-toned color. Sodium phosphate tablet OsmoPrep (USA: OsmoPrep®, France: Colokit®) is used for colonoscopy preparation, occasionally employed in patients that do not wish to ingest the large volumes of liquids otherwise required for the procedure. The drug in its solution preparation (Phosphosoda) is well known to cause colonic aphthous ulcers and focal active colitis. The tablets instead cause deposits in the stomach where they mimic calcinosis and iron-pill injury²⁶. The injury is of the gastropathy/erosive type. The deposition occurs in the gastric superficial lamina propria where it appears similar to crushed pill fragments, purple to black, less often translucent, less than 100 microns in size (Fig. 11). OsmoPrep is von Kossa stain positive (von Kossa stains the phosphate moiety) but alizarine red negative. This staining pattern distinguishes OsmoPrep from gastric calcinosis in which calcium is reactive for both stains²⁶.

Fig. 10. Microcrystalline cellulose appears as transparent in A (H-E stain) B) and brightly birefringent under polarized light (B). Courtesy of Dr. R. Gonzales Univ. of Rochester, Rochester NY, USA).

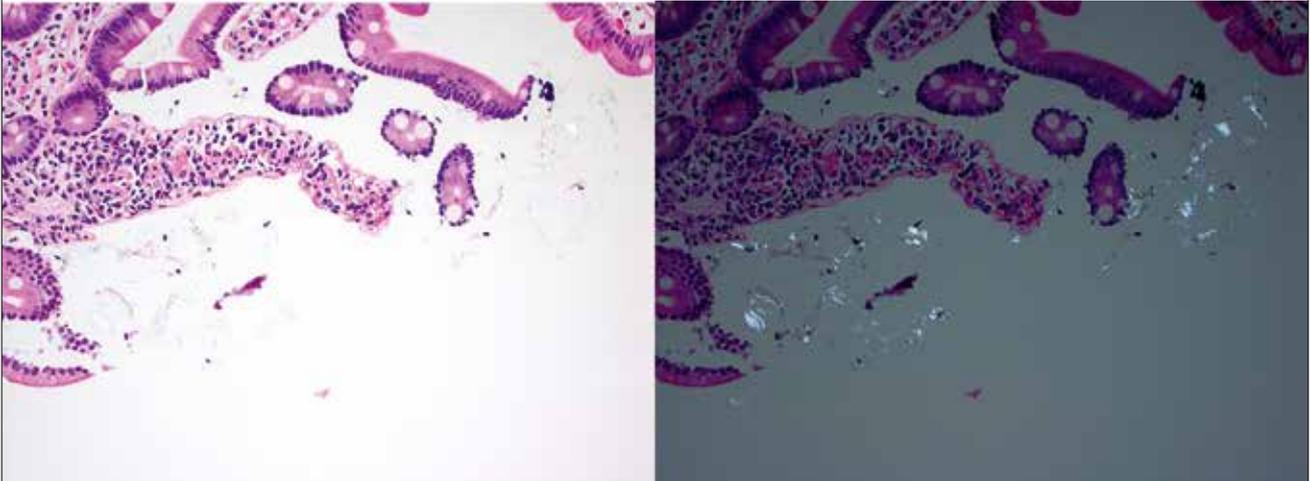
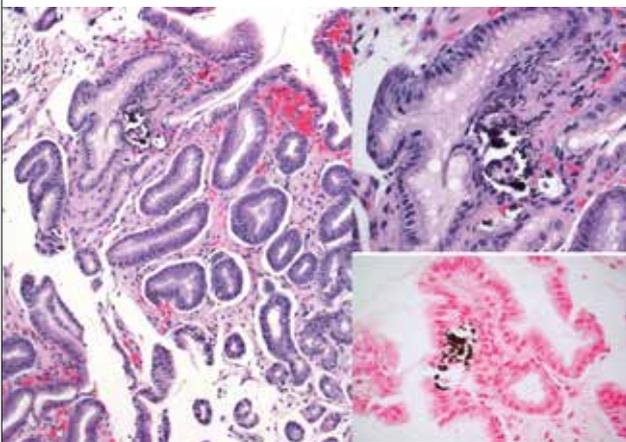


Fig. 11. OsmoPrep deposition in superficial gastric lamina propria. The bottom right figure shows positivity for Von Kossa stain. Courtesy of Dr. K. Matsukuma, Univ of California, Davis, CA, USA).



Finally, the pathologist should be aware of the possibility of *multiple* compounds deposits and crystals being present in the same patient. The clinical background in which the drugs are used may also heighten the need to look for and/or exclude associated conditions (e.g. amyloid in case of CRF with GI resins crystals).

KEY POINT #2:

The pathologist can be decisive and recognize drugs in H-E stained slides. Identification is clinically useful.

Some drug effects are traps we must know about

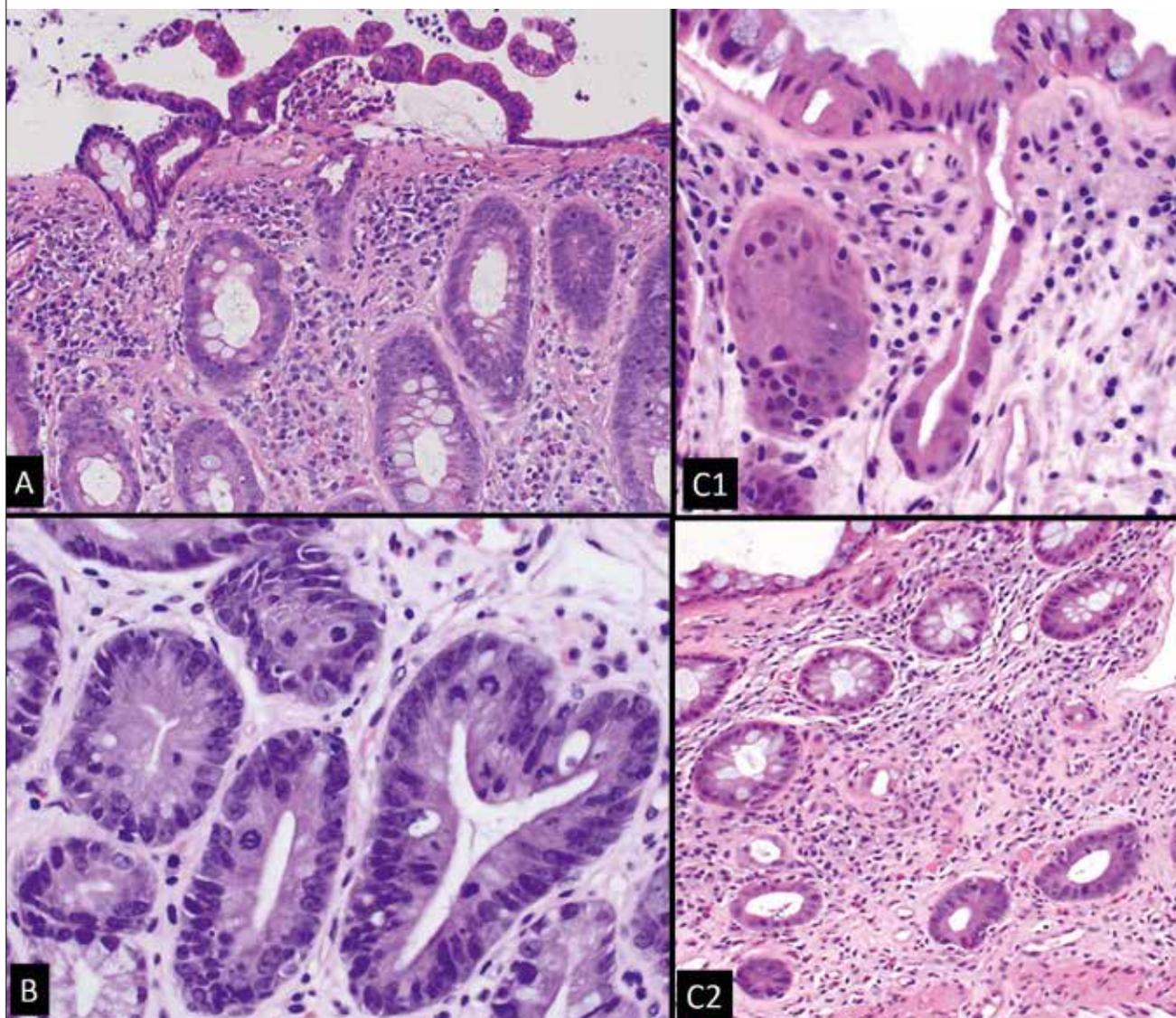
Olmesartan medoxomil, a widely-prescribed angiotensin II receptor blocker antihypertensive drug, is used by millions of patients, a minuscule minority of them develops a significant DIGI after months to years of exposure²⁷. Olmesartan can cause sprue-like enteropa-

thy especially in elderly patients. Partial or total villous blunting, increase in IELs and collagenous enteritis are reported frequently in this DIGI. The stomach and colon have similar findings consisting of lymphocytic and collagenous gastritis and colitis in isolation or associated with enteropathy (Fig. 12A). A detailed exam of the cases in the literature shows however that the occasional patient may sometime present without duodenal IELs increase (Fig. 12A) in olmesartan-induced villous atrophy, a significant difference with celiac disease²⁸.

The recognition of this DIGI is perhaps the most important of all. The patients are often hospitalized with uncontrollable diarrhea and electrolytes disorders, typically with a diagnosis of sero-negative celiac disease; “suspicious for lymphoma” is another preliminary diagnosis that will also be given due to the refractoriness to all therapies and the severity of symptoms. The suspension of olmesartan will prevent malnutrition and expensive testing, and is spectacularly effective in relieving the symptoms in few days and in restituting the morphology to normal, or almost normal, in few months. Symptoms do recur after reintroduction of olmesartan in the few cases in which this was attempted²⁸. Of note other members of the Angiotensin Receptor Blocker (ARB) family are capable of causing severe enteropathy and enterocolitis (e.g. Valsartan and Telmersartan) and Losartan (Dr De Marco personal communication)²⁸⁻²⁹. The dramatic enteropathy certainly dominates our clinical interaction with ARBs DIGI, however it is likely that ARBs have milder histological presentations (e.g. increase in chronic inflammation, isolated duodenal or colonic IELs increase)²⁸⁻³⁰.

Taxanes (Paclitaxel, Docetaxel, Cabazitaxel) used in cancer patients (breast, ovary, digestive and prostate cancers) disrupt mitotic tubules preventing tubule depolymerization (mitotic arrest-drugs) and have a direct antitumoral apoptotic effect (Docetaxel in particular). Taxanes can mimic dysplasia anywhere in the GI and to perfection in mucosa of Barrett’s esophagus. Atypical

Fig. 12. A illustrates a collagenous enteritis due to olmesartan. Notice how IELs are not prominent in this case, an event occurring in a minority of cases. In B is Taxol effect in Barrett's esophagus, a mitosis with a central bar in it is present in the center. C1 and C2 show mycophenolate colitis. In C1 eosinophilic exhausted epithelium stretches along a injured crypt. In C2 the appearance of the mucosa with crypts drop out, distortion and damaged crypts is present.



nuclei with numerous mitoses (some appearing as ring mitoses, some others with a central bar) and increased apoptosis are the results of taxanes intake (Fig. 12B). To help in the differential diagnosis between true dysplasia and taxanes it has been reported how taxanes affects only the proliferative areas of the glands and that hyperchromasia and nuclear pleomorphism are absent in taxanes effect³¹. The differential diagnosis remains highly difficult in Barrett's esophagus or other conditions prone to dysplasia and exposed to taxanes: only awareness of this DIGI and clinical correlation will help prevent this pitfall.

Mycophenolate is used in solid organ graft maintenance therapy and in autoimmune disorders (e.g lupus, psoriasis, myasthenia gravis). Mycophenolate colitis is well described²⁻⁴: the main features are (Fig. 12 C) architectural disarray of the mucosa with crypts drop out and

“exhausted” apoptotic crypts (that is: thinned stretched eosinophilic epithelium around a dilated/damaged-appearing crypt (DDC) with eosinophilic luminal debris and increased apoptotic bodies)^{4,32,33}. Occasionally mycophenolate colitis is ischemic in appearance, in individual cases the colitis is worse in the proximal colon. Of note the colitis can have skip areas further mimicking Crohn's disease to the unaware. In the small intestine villous atrophy and inflammation due to mycophenolate can mimic celiac disease in the individual case. The DDC pattern of mycophenolate is reminiscent of, and needs to be distinguished from, cytomegalovirus infection and especially GVHD. These conditions must be excluded due to vastly different therapies. Star et al.³⁴ summarized features to help distinguish the two as follows: mycophenolate colitis features much more prominent lamina propria inflammation with eosinophils than

GVHD, while GVHD displays endocrine nests and apoptotic microabscesses more commonly than mycophenolate.

KEY POINT #3:

The most relevant pitfalls due to DIGI are those related to olmesartan and other ARBs (vs celiac disease and/or collagenous enteropathy), mycophenolate (vs. GVHD and CMV) and taxanes (vs. dysplasia).

Oncology is a fertile ground for DIGI

New oncologic therapies are not exempt of side-effects in GI. DIGI provoked by the recently developed immune checkpoint inhibitors and Phosphatidylinositol-3-Kinase (PI3K) inhibitors will be analyzed here.

Immune checkpoint inhibitors. Under this category are CTLA-4 (cytotoxic T-lymphocyte associated protein-4) inhibitors (ipilimumab and tremelimumab) and Programmed Death-1 receptor inhibitors (PDI) (such as pembrolizumab, nivolumab and atezolimumab that targets the PD-1 ligand). These two classes of inhibitors are sometimes used together in modern oncology therapy. The severity of the GI side effects is higher after CTLA-4 inhibitors^{35 36 41}.

CTLA-4 is a receptor whose activation inhibits cytotoxic T-cells. Inhibitors of CTLA-4 (I-C) remove this inhibition and prolong cytotoxic T-cells activation and action on tumor cells. I-C are approved for the treatment of advanced melanoma, they are under investigation in the treatment of non-small cell carcinoma of the lung, as well as prostate, renal and ovarian carcinoma, and in mesothelioma. The mechanism of action of I-C leads to loss of systemic tolerance and a host of immune-related disorders including DIGI. Between 20 and 50% of patients suffer GI side effects, the most common being watery diarrhea appearing within 6 weeks into treatment sometimes as early as few days from the beginning of the therapy³⁵.

Life threatening colitis is seen in 16% of patients³⁶. Less than 1 percent of patients suffer serious intestinal side effect or death³⁶. The endoscopic appearance of diffuse colitis was seen in 21% of patients in a study by Beck et al.³⁷. Ipilimumab offends also stomach and small intestine, sometimes in isolation. Endoscopy shows granularity, exudate, and erosion/ulcers but can be entirely normal even though colitis is present: biopsies must always be obtained. The histopathological findings^{38 39} are similar throughout the intestine. The histology demonstrates villous blunting, diffuse chronic inflammation of mucosa, and increase in apoptosis, rare neutrophilic cryptitis, and intraepithelial lymphocytosis. They resemble autoimmune enterocolitis, an otherwise utterly rare disease in adults. The diagnosis of AIE in an adult should be made after DIGI has been excluded. The process may occasionally suggest IBD on a superficial observation, however in the colon there are no classic IBD findings such as basal plasmacytosis and crypts distortion. As a reminder, classic IBD would not have severe

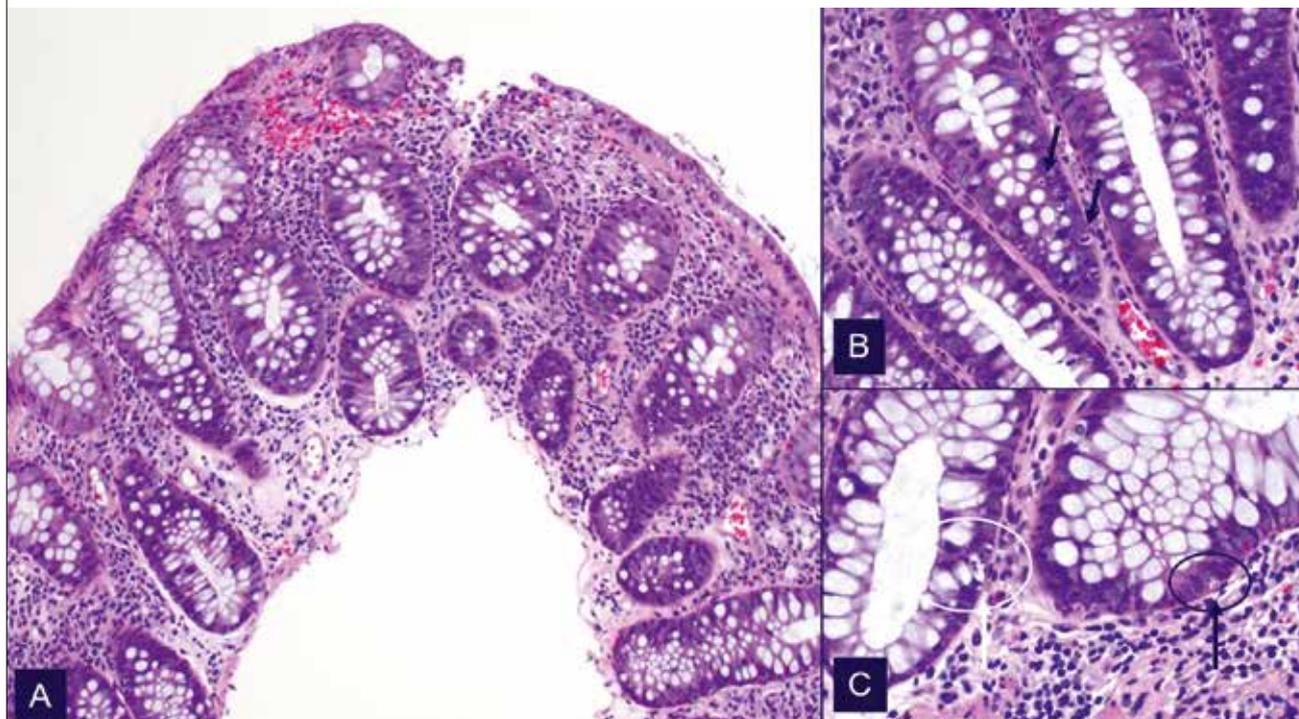
apoptosis or marked increase in IELs (Fig. 13). Rare is lymphocytic colitis and even rarer is ipilimumab associated lymphocytic proctitis of the colon. An exceptional case from Mayo Clinic showed the activation of a latent celiac disease into overt disease after ipilimumab⁴⁰.

PD-1 receptor activation prevents cytotoxic T-cell activation by self-antigens. Tumors use this mechanism to defuse the antitumoral immunological response. PD-1 inhibitors (PI) unbridle the T-cell response to malignancies. PI are employed in melanoma, urothelial carcinoma, non-small cell carcinoma of the lung, renal carcinoma and mismatch repair deficient colorectal carcinoma. It is not surprising that the enhanced T-cell response is accompanied by a series of side effects that appear to be immune-related. PIs cause mild watery diarrhea in 20-30% of patients, approximately 6 weeks into treatment⁴¹ (severe in less than 10% of cases), and other GI symptoms (nausea vomiting, abdominal pain occult blood in stool. The endoscopy shows erythema friability and aphthous ulcers. The histology of PI injury has been recently described in 19 patients⁴². Any portion of the GI was found affected in at least one patient. The upper GI showed increased mononuclear cells in the lamina propria of stomach and duodenum, villous blunting, increased eosinophils, neutrophilic villitis, neutrophils in foveolar epithelium. On the other hand, increased apoptosis was less common. Similar findings were seen in the terminal ileum. Distortion of mucosal architecture was not a feature of PI DIGI. The colon had similar findings with, however, more common apoptotic bodies and, interestingly, ischemic colitis. Increased intraepithelial lymphocytes were seen in both upper and lower GI. Collagenous colitis was seen in one case. An unusual finding was the development of well-formed granulomas associated with crypt ruptures.

Phosphatidylinositol-3-kinase (PI3K) inhibitors. PI3K are a family of kinases that regulates several cancer cells functions. Idelalisib (Zydelig[®]) is a selective inhibitor of the PI3K delta isoenzyme that promotes apoptosis in cells of hematopoietic malignancies. Idelalisib is used in therapy of relapsed or refractory chronic lymphocytic leukemia, small lymphocytic lymphoma and follicular lymphoma. Idealisib therapy can cause immune-mediated toxicities affecting liver and colon⁴³, side effects that may require cessation of the therapy. Diarrhea is usually watery and appears in 20-45% of patients⁴⁴. Early diarrhea (in the first two months) is responsive to symptomatic therapy without need of stopping the drug. Late diarrhea is considered a symptom of Idelalisib-induced autoimmune enterocolitis and generally requires discontinuation of the drug⁴⁴. Endoscopy of the colon often reveals nothing of relevance or, in a minority of cases, pseudo-membranes, aphthous ulcers and erythema.

Histological changes in the small bowel include increase in mononuclear cells infiltrate in lamina propria, increased apoptosis, villous atrophy, and increased intraepithelial lymphocytes, less commonly reduced gob-

Fig. 13. Ipilimumab colitis. Chronic inflammation in colon mucosa in A but no evidence of chronic architectural injury. In B and C the arrows and circles highlight the apoptosis and the scattered neutrophils in epithelium. A similar picture could originate from PD1 or PI3k inhibitors colitides. From G De Petris et al. *Int J Surg Pathol* 2014 2:120-128.



let cells, and acute inflammation⁴⁵. Histological changes in the colon go under the umbrella of several injury patterns: GVHD pattern, IBD pattern, acute colitis pattern, and intraepithelial lymphocytosis pattern. Among the constitutive abnormalities, apoptosis and neutrophilic inflammation are uniformly found in every case. Interestingly dilated/damaged exploded/apoptotic crypt with luminal debris with few neutrophils is often part of the inflammatory process^{45 46}. These changes mimic other immunomodulators and mycophenolate effects and conditions such as Common Variable Immunodeficiency in the GI, autoimmune enterocolitis, GVHD and CMV colitis.

It appears that modulation of immunological mechanisms causes an overall repetitive pattern of injury in the various situations and drugs listed above. This allows a generalization into our final key point:

KEY POINT #4:

Apoptosis, increase inIELs, mild neutrophilic cryptitis and chronic inflammatory infiltrate are the common traits of colitis due to immune checkpoint inhibitors, PI-3-Kinase inhibitors and mycophenolate. Villous shortening and IELs increase are the common traits of these drugs enteropathy. The overall pattern of immunomodulators DIGI has significant overlap with autoimmune enterocolitis, celiac disease, Common Variable Immunodeficiency, even IBD. In an oncology patient, these drugs effects should be excluded before alternative diagnoses are offered. CMV and GVHD, in the appropriate clinical setting, must also carefully be considered and investigated.

Final words

This review intended to provide direct and useful messages and reflections in a field that by its variegated nature is otherwise of difficult synthesis. Key points proposed integrate clinical and pathological data making the pathologist a crucial element in DIGI recognition and appropriate therapy. The information and ideas conveyed have been collected from personal experience and literature review, hopefully they enlighten the reader with regards to DIGI and provide means to avoid the main DIGI traps and pitfalls. The future will hold undoubtedly new challenges from DIGI for the GI pathologist. Old drugs may be replaced by new and safer ones (see SPS being replaced by less dangerous drugs for example), but unwanted effects of new drugs will need to be ascertained. We have not mentioned several drug-related effects (e.g Colchicine vs taxanes, Dasatinib, TNF antagonists and many more): we wanted few concepts to be in the forefront not an encyclopedia of DIGI; having said that we also think that a repository of the pathology of DIGI (similar to that of Drug Induced Liver Injury) would certainly benefit the pathology community facing this ever increasing and complex challenge.

Appendix

Drugs mentioned in the paper and relative brand names: The commercial names listed are by no means intended to be complete. E.g. multiple agents may be present together in association with the offending drug considered here for DIGI (for example with olmesartan). The list is

only meant to be helpful to recognize some of the most commonly used name brands associated with the drugs mentioned in the paper.

NSAIDs (a very long list of aspirine and COX inhibitors could be entered here, please refer to textbooks or websites), doxycycline (Vibramicin® and many other brand names); Yttrium-90 loaded particles (Syrtext SYR-spheres®); Iron supplements (several formulations and brand names), Sodium polystyrene sulphate (Kayexalate®); Patiromer (Veltassa®); Sevelamer (Rengela®, Renagel®); Cholestyramine (Questran®, Prevalite®); Colesevelam (Welchol®); Cholestipol (Colestid®); Lanthanum carbonate (Fosrenol®); Sodium phosphate tablets (OsmoPrep®), Olmesartan (Benicar®, Azor® etc); Valsartan (Diovan®, Entresto® etc.); Ilbesartan (Avapro®, Karvea®, Aprovel®); Losartan (Cozaar®, Hyzaar®); Taxanes: Paclitaxel (Taxol®, Onxol®, Abraxane®); Docetaxel (Taxotere®, Docefrez®), Cabazitaxel (Jevtana®); Mycophenolate (Mycophenolate mofetil: Cellcept® and Mycophenolate sodium: Myfortic®); Ipilimumab (Yervoy®); Tremelimumab; Pembrolizumab (Keytruda®); Nivolumab (Opdivo®); Atezolimumab (Tecentriq®); Idelalisib (Zydelig®).

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