Envoi SPECIALIST PATHOLOGISTS inside insights

Update No.4 – 2018 Dr Christophe Rosty

GIT and hepatic complications of immune checkpoint inhibitors

Immune checkpoint inhibitors are recently developed cancer immunotherapy drugs that enhance T-cell mediated immune response leading to tumour cell destruction. Idelalisib is a different immunotherapeutic agent promoting apoptosis in haematological malignancies.

Drug	Target	Indication
Ipilimumab Tremelimumab	CTLA-4	Melanoma
Nivolumab Pembrolizumab	PD-1	Melanoma, non-small cell lung carcinoma, hepatocellular carcinoma, mismatch repair deficient-colorectal carcinoma, renal cell carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma
Atezolizumab Durvalumab	PD-L1	
Idelalisib	PI3Kδ	Chronic lymphocytic lymphoma/small lymphocytic lymphoma, follicular lymphoma

All these drugs can trigger autoimmune type complications (immune-related adverse events) in any organ system, most commonly the skin, GIT, endocrine organs and liver.

1. GIT complications:

Clinical presentation:

- Diarrhoea of any grade, abdominal pain, PR bleeding
- More common and more severe for anti-CTLA-4 than anti-PD-1
- Onset usually 4-10 weeks after the first dose and after skin reaction
- Colonic perforation in 1% for anti-CTLA-4 drugs

Colonoscopy:

- loss of vascular pattern, erythematous mucosa with multifocal ulcerations in various parts of the large bowel
- Frequent involvement of the upper GIT

Histology:

- combination of acute infective-type colitis (inflamed lamina propria, neutrophilic cryptitis) and immune-type injury (apoptotic bodies, intraepithelial lymphocytes)
- non-specific gastritis
- non-specific duodenitis with villous blunting

Differential diagnosis:

- Inflammatory bowel disease, infective colitis, GVHD, other drug-induced reaction

Management:

- Grade 3 diarrhoea: cease drug, systemic steroids +/- infliximab
- Grade 4 diarrhoea: permanently cease drug, systemic steroids +/- infliximab, emergency colectomy

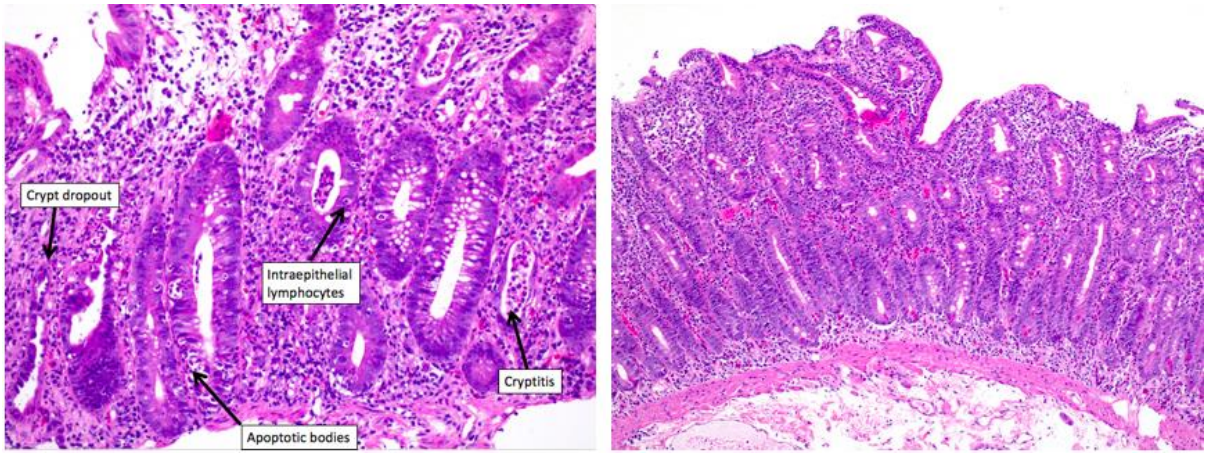

Figure 1. Nivolumab-induced colitis (left image); duodenitis with villous blunting and intraepithelial lymphocytosis secondary to nivolumab (right image).

2. Hepatic complications:

Clinical presentation:

- asymptomatic increase in LFTs: increased AST/ALT and mildly increased bilirubin
- present in 3-10% of treated patients

Histology:

- Most commonly autoimmune hepatitis-like pattern: active panlobular and portal hepatitis with prominent sinusoidal lymphohistiocytic infiltrate for anti-CTLA-4.
- Less commonly centrilobular hepatitis, biliary pattern of injury, endothelialitis, steatohepatitis

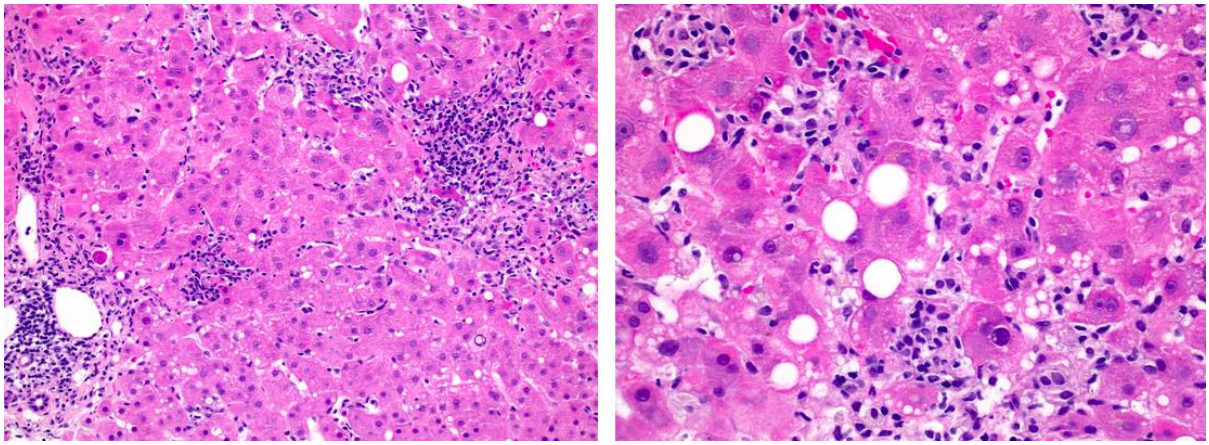

Figure 2. Portal and panlobular hepatitis in a patient treated by ipilimumab and nivolumab, with predominance of lymphocytes and histiocytes in the lobule (right image).

Differential diagnosis:

- autoimmune hepatitis, acute viral hepatitis, DILI to other drugs

Management:

- Grade 3 hepatitis (AST/ALT 5-20 x, and/or total BR 3-10 x): cease drug, systemic steroids +/- other immunosuppression (MMF or 6-MP)
- Grade 4 hepatitis (AST/ALT >20 x, and/or total BR >10 x): permanent cease drug, higher dose systemic steroids +/- other immunosuppression

References

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