Author/s:
Shankar, S;Oliver, MR

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Primum non nocere: Minocycline-induced liver injury in a teenager

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Key Points

1. It is important to have a high degree of suspicion for drug related toxicity in every patient with liver dysfunction and a detailed drug history with emphasis on the commonly implicated drugs should be elicited.
2. Minocycline, a tetracycline widely used for treatment of acne is known to cause hepatotoxicity with a variable latency and can occasionally occur after cessation of drug. This can result in failure to identify minocycline as the inciting agent.
3. It is necessary to follow up patients with a diagnosis of drug induced hepatotoxicity until complete resolution of abnormal liver biochemistry. This is to ensure that they do not have an underlying chronic liver disease or develop chronic drug induced liver injury.

Case Report

A 15-year-old girl presented with 8-day history of fever, rash and abdominal pain. She did not report any localising symptoms, jaundice, bleeding or altered sensorium. On enquiry, she reported treatment with minocycline 50mg BD for acne, for 4 weeks prior to onset of illness and experienced symptoms a couple of days after cessation of minocycline. This had also coincided with a vacation in Northern Queensland. Her past medical history was unremarkable and her immunisations were up-to-date.

On examination, she looked unwell, was febrile, tachycardic, but normotensive. She had a generalised erythematous maculopapular rash with few petechiae. She was anicteric with cervical and axillary lymphadenopathy, but no peripheral oedema or stigmata of chronic liver disease. Abdominal examination revealed tender hepatomegaly with a palpable left lobe and an enlarged spleen. There was some free fluid as evidenced by bilateral flank dullness. The rest of her physical examination was unremarkable.

Blood investigations revealed mild normocytic anaemia with neutropenia, reactive lymphocytosis, eosinophilia (Table 1) and thrombocytopenia. Liver function tests (LFT) showed a

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predominant “hepatitis” picture with normal conjugated bilirubin and low albumin (Table 1). She had a mildly deranged International Normalised ratio (1.3) which corrected with a single dose of intravenous vitamin K and subsequently remained normal throughout the course of illness. Other coagulation parameters (APTT, fibrinogen) were normal. An Ultrasound abdomen revealed mild hepatomegaly, significant splenomegaly, intraabdominal lymphadenopathy and mild to moderate ascites.

At the time, several conditions were considered as a cause of her clinical picture, including acute viral hepatitis, Gram negative bacteraemia or meningococcal sepsis, Autoimmune hepatitis, Haemophagocytic Lymphohistiocytosis, Drug induced hypersensitivity, Wilson’s disease, acute decompensation of an underlying chronic liver disease or an infiltrative disorder such as histiocytosis/lymphoid malignancy. Blood investigations looking for the aetiology are summarised in table 2. Her paracetamol levels were just above the upper limit of normal and she received N-acetyl cysteine infusion given her significant transaminitis.

In view of worsening LFTs, liver biopsy along with a skin biopsy were performed. Liver biopsy was suggestive of acute portal and lobular hepatitis with lymphocytic and abundant eosinophilic infiltrate. No features suggestive of chronic liver disease or autoimmune hepatitis were evident. The histological features of skin biopsy were consistent with spongiotic drug eruption.

Once the diagnosis of drug induced hypersensitivity was established on liver and skin biopsy, she was started on intravenous steroids and discharged home on tapering doses of oral steroids. At a follow-up visit 6 months after discharge, she was clinically well with no evidence of persisting organomegaly and normal LFT.

Discussion

Drug induced liver injury (DILI) is an important but under-recognised cause of liver disease in children and contributes to about 20% of Paediatric acute liver failure.[1] The incidence of DILI in children is unknown, but the most recent adult study estimated 19.1 cases in 100,000 people annually.[2]

DILI can be a spectrum ranging from asymptomatic deranged liver function tests to acute liver failure. Classical example of intrinsic/predictable DILI is acetaminophen induced liver damage. Drug

related liver toxicity which is dose-independent, less consistent, and occurring in susceptible individuals with variable latency is defined as idiosyncratic DILI.[2] The diagnosis of idiosyncratic DILI is challenging as it is essentially a diagnosis of exclusion. A careful drug history should be obtained in every child with deranged liver function tests including use of prescription, over-the-counter, herbal and alternative medications for upto six months prior to onset of liver dysfunction.[2] Knowledge of commonly implicated agents and their patterns of liver injury can aid in history-taking (Table 3). Acute viral hepatitis can masquerade as DILI and needs to be ruled out conclusively.[3] Other competing aetiologies such as metabolic and autoimmune causes of liver disease should be considered. Our patient was investigated extensively for infectious and immune causes of hepatitis before being diagnosed as DILI.

Minocycline, a tetracycline widely used in the treatment of acne vulgaris in adolescent teenagers has immense potential for hepatotoxicity. The DILIN (Drug-induced liver injury network) prospective study observed minocycline to be the single most commonly implicated antimicrobial in children as opposed to Amoxycillin-clavulanate in adults.[4] There have been several case reports of Minocycline-induced liver dysfunction ranging from acute hepatitis, DRESS, autoimmune hepatitis to acute liver failure resulting in death/transplantation.[5] Minocycline can result in two types of hepatotoxicity- 1) Hypersensitivity hepatitis which develops within days to weeks (1-3 months) of minocycline use with fever, rash, lymphadenopathy, peripheral eosinophilia and exfoliative dermatitis, 2) Drug induced autoimmune hepatitis akin to chronic autoimmune hepatitis (AIH) with lupus-like symptoms, which develops months to years after minocycline use and can occasionally occur after stopping the drug.[1,5] Our patient was investigated for possible autoimmune hepatitis (de novo or drug-induced), however neither her serology nor liver histology was suggestive. Although liver biopsy is not mandatory for diagnosis, it is recommended if there is persistence or worsening of abnormal liver biochemistry despite cessation of the drug or when AIH is suspected.[3] Steroids were commenced in our patient due to systemic features. Small uncontrolled studies have demonstrated benefit of steroids in severe hepatitis with systemic features[1,6], however there are no controlled trials ascertaining their efficacy. A Cochrane review regarding safety and efficacy of minocycline noted an increase in the risk of liver dysfunction associated with minocycline use, but overall incidence was rare - 1.04/ 10,000 exposed

person–months with an odds ratio of 2.1.[7] Routine monitoring of liver functions was not recommended except in patients receiving long-term treatment. With advances in pharmacogenomics, it is possible to identify individuals at risk of severe drug reactions. Urban et al recently demonstrated that individuals who are HLA-B∗35:02 carriers are at increased risk of developing minocycline related liver injury.[8] Re-exposure to hepatotoxic drugs is strongly discouraged particularly if there is a significant rise in transaminases (>5 X ULN), or jaundice.[3] In our case, an adverse drug reaction report was completed and she was advised to avoid tetracyclines lifelong.

This case report highlights the importance of a detailed drug history when faced with a patient with liver dysfunction and the significant hepatotoxic potential of a widely used drug such as Minocycline.

MCQs

1) All the following statements are true regarding idiosyncratic DILI except
   A. It can be diagnosed without a liver biopsy
   B. Onset of symptoms of DILI can occur after stopping the drug
   C. Liver function tests always improve after cessation of the offending drug
   D. Cholestatic DILI takes a longer time to recover than hepatocellular DILI
   E. Rechallenge of offending drug is best avoided

   Ans. C Liver function tests may not always improve soon after cessation of drug – although the hallmark of treatment of drug-induced liver injury is withdrawal of offending drug. Occasionally, the onset of DILI symptoms can occur after cessation of the drug, persist for a long time despite cessation of the drug resulting in Chronic DILI. Re-administration of hepatotoxic drug is not recommended unless it is a life-saving drug without any alternatives.

2) A 16-year-old girl is referred by her GP for deranged LFTs when she was investigated for symptoms of fatigue. On enquiry, she has been receiving treatment for acne with minocycline on and off for the last 1 year. Her physical examination is unremarkable. Her LFTs are as below -

Bilirubin- 5(0-15µmol/L), ALT 256 (5-30 IU/L), GGT 102 (0-40 IU/L), Total protein 82(57-80 g/L), Albumin 32(33-47 g/L). How would you investigate the cause of deranged LFTs?

A. Viral serology for Hepatitis
B. Autoimmune markers and Immunoglobulin levels
C. Ceruloplasmin and Iron studies
D. All the above
E. None of the above

Ans. D Although Minocycline can result in the clinical picture as described above, it is important to remember that it is a diagnosis of exclusion and infectious, autoimmune and metabolic causes need to be ruled out conclusively prior to making a diagnosis of Drug-induced liver injury.

3) Minocycline induced Autoimmune hepatitis (AIH) differs from de-novo AIH as follows
   A. It is histologically different from de-novo AIH
   B. It is seronegative
   C. It always improves following cessation of drug
   D. It requires long term immunosuppression
   E. It has a favourable prognosis

   Ans. E. Drug-induced AIH (DI-AIH) is very difficult to distinguish from De novo or idiopathic autoimmune hepatitis (iAIH) and may fulfil serological and histological criteria as laid down by International Autoimmune Hepatitis Group (IAHG). It may or may not improvement with cessation of drug. However, it is differentiated from iAIH by its favourable prognosis, requiring only a brief period of immunosuppression. If a patient diagnosed to have DI-AIH needs long term immunosuppression, it should prompt the physician to reconsider the diagnosis.

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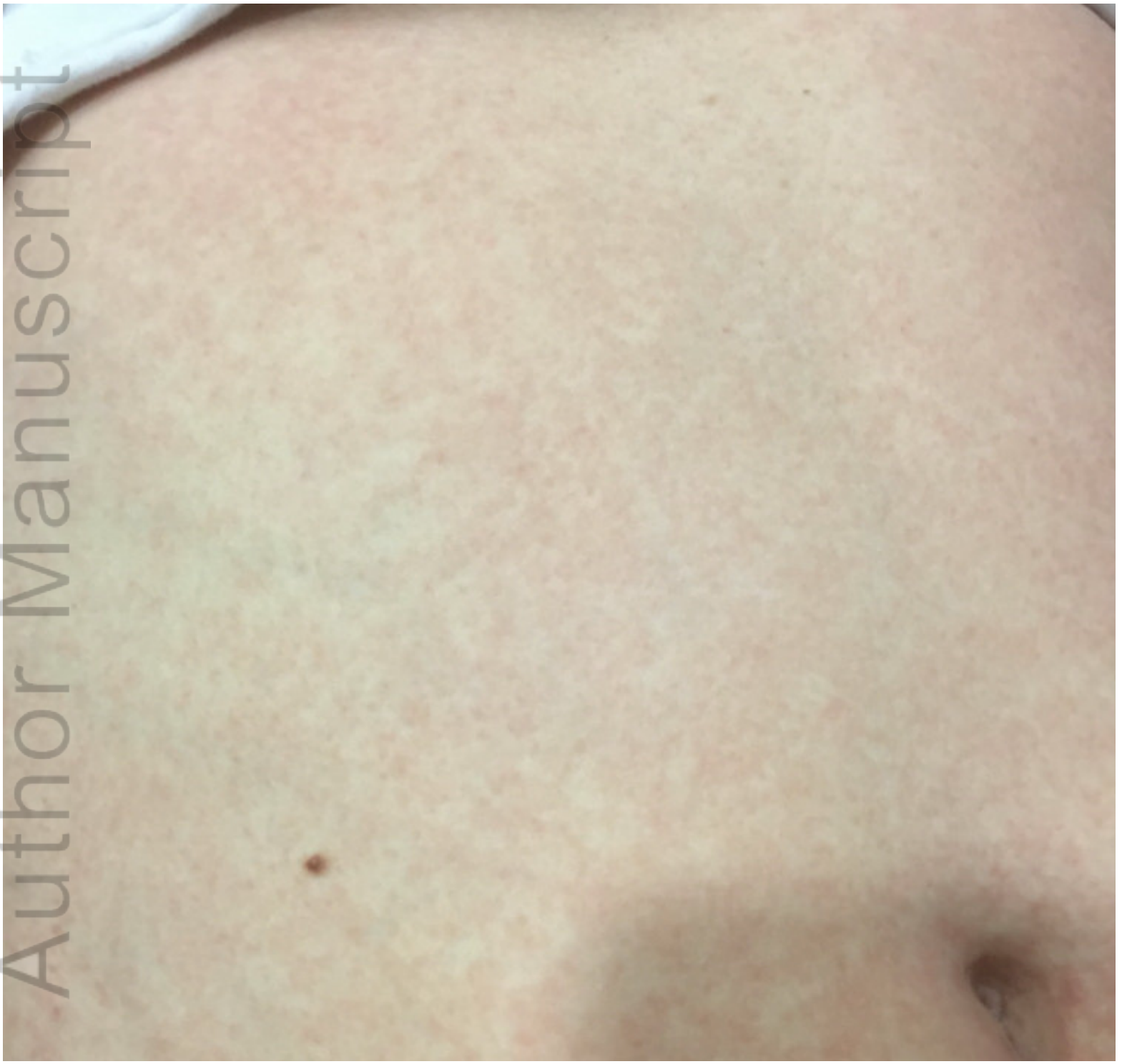

DILI clinical photo.PNG

Table 1 – Trend of LFTs, WCC (white cell count) and eosinophil count

	Day 1	Day 2	Day 3	Day 4	Day 8 Discharged	6 months from discharge
ALT (5-30 IU/L)	688	1302	673	514	249	20
GGT (0-40 IU/L)	281	266	304	249	189	11
Total Protein (57-80 g/L)	52	46	55	54	72	68
Albumin (33-47 g/L)	29	24	30	29	40	43
WCC ($4.5\text{-}11X10^9$/L)	6.3	5.9	4.9	N/A	5.8	4.9
Eosinophil count ($0\text{-}0.5X10^9$/L)	0.5	1.24	0.54	N/A	0.03	0.05

Table 2 – Aetiological workup

Infectious	Hepatitis A, B, C, E serology, EBV, CMV serology, HHV 6, HSV, Adenovirus, enterovirus PCR - negative. Serology for dengue, leptospira, Bartonella henselae, Brucella, Rickettsia were negative.	
Immune- mediated	ANA, Anti LKM, Smooth muscle Ab negative, Total IgG normal	
	Fibrinogen	Normal
	Soluble CD25	23087 (186 - 2678 pg/ml)
	Triglycerides	Normal
Drugs	Paracetamol levels	149µmol/L (<120µmol/L)
Chronic Liver Disease with acute decompensation	Wilson's – Normal Ceruloplasmin (after acute hepatitis resolved) Alpha1AT levels – Normal	

Table 3 – Common hepatotoxic drugs and their patterns of injury

Antibiotics	Pattern of liver injury[¶]
Amoxicillin- clavulanate	Cholestatic, can be hepatocellular, onset after cessation of drug
Anti –TB drugs (Isoniazid, Rifampicin)	Acute hepatocellular, onset after cessation of drug
Fluoroquinolones	Variable: Hepatocellular, cholestatic or mixed
Macrolides	Hepatocellular, can be cholestatic
Minocycline	Hepatocellular, resembles Autoimmune hepatitis
Nitrofurantoin	Hepatocellular, resembles Autoimmune hepatitis
Antiepileptics	
Valproate	Reye-like syndrome, hyperammonemia, acute hepatocellular
Phenytoin	DRESS[†] can be hepatocellular or mixed
Carbamazepine	DRESS
Lamotrigine	DRESS
Miscellaneous	
Methotrexate	Liver fibrosis, fatty change
Azathioprine	Cholestatic or Hepatocellular
Sulfasalazine	Mixed, cholestatic or hepatocellular

[¶] Pattern of injury defined by R value, R= ALT/ULN ÷ALP/ULN (R>5 hepatocellular, R<2 Cholestatic, R 2-5 Mixed) (ALT -Alanine transaminase, ALP- Alkaline phosphatase, ULN-upper limit of normal)

[†] DRESS – Drug reaction, eosinophilia with systemic symptoms

Adapted from ACG Clinical Guideline: The Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury in the American Journal of Gastroenterology.[Error! Bookmark not defined.]

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Authors:

1) Dr. Sahana Shankar, MD

Department of Gastroenterology, Hepatology and Clinical nutrition, Royal Children's Hospital

2) Prof. Mark R Oliver, MBBS, FRACP, MD

Department of Gastroenterology, Royal Children's Hospital

Murdoch Children's Research Institute

Department of Paediatrics, University of Melbourne

Institute: Royal Children's Hospital, 50 Flemington road, Parkville, VIC 3052

Corresponding Author:

Dr. Sahana Shankar

Royal Children's Hospital,

50, Flemington Road,

Parkville, VIC 3052

Email: Sahana.shankar@rch.org.au

Ph : 93454739