rent episodes of cholangitis. The patient had undergone four previous endoscopic retrograde cholangiopancreatographys (ERCP), a sphincterotomy had been performed and at her most recent ERCP, 28 months prior to this presentation, a 6Fr 7 cm pigtail biliary stent had been inserted.

Examination revealed a distended abdomen with mild generalized tenderness. An irregular mass was detected in the right lower quadrant. Abdominal radiographs showed small bowel obstruction with the stent in the right iliac fossa.

At laparotomy, following extensive adhesionolysis, a 30 cm segment of edematous, thick-walled terminal ileum was noted. The stent could be palpated through the thickened bowel wall. This segment was resected (Fig. 1) and a primary end-to-end anastomosis was performed.

Increasing indications for stent insertion has contributed to a growing number of reports relating to unusual distal intestinal complications. Particularly susceptible it seems is sigmoid diverticular perforation,[1] and perforations of the small bowel[2] where there is some mechanical impediment to normal emptying, such as the case of perforation in an incarcerated hernial sac,[3] a parastomal hernia,[4] and in the ileum of a patient with dense intra-abdominal adhesions.[5] In each of these cases the offending stent had been of the relatively rigid straight plastic variety.

Straight plastic polyethylene stents have been adapted to decrease the risk of migration by including side flaps or barbs. By their design, the double ended pigtail stents are less likely to move, and have been shown to have a low migration rate, but a higher rate of early failure. It is likely that in the uncommon event of migration of a pigtail stent that its pliable, soft plastic would typically allow passage unimpeded through the intestinal lumen. Obstruction of normal bowel peristalsis may contribute to preventing a stent from negotiating part of the lumen; certainly in our case dense intra-abdominal adhesions may have had a part to play.

Straight plastic stents, previous intra-abdominal surgery, hernia and diverticular disease are risk factors for complications occurring in distal stent migration. These should be considered when inserting biliary endoprosthesis and in the subsequent follow-up. They may influence the early management of an asymptomatic patient with known stent migration. An aggressive pre-emptive approach may be an attempted endoscopic retrieval of a stent or the repair of a hernia prior to stent insertion.

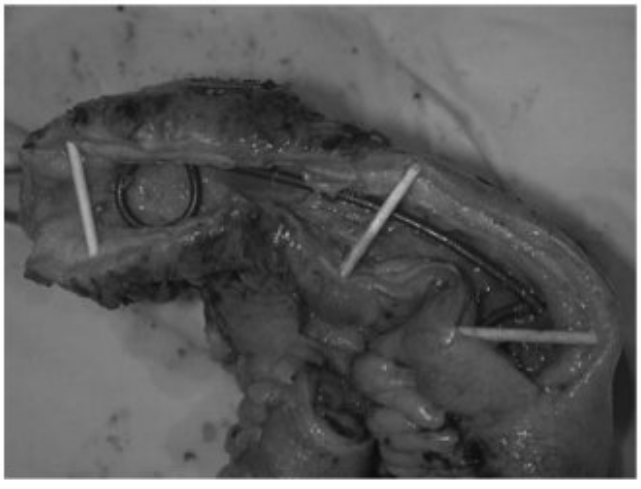

Figure 1 Resected small bowel with stent *in situ*.

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Predisposition of antituberculosis drug induced hepatotoxicity by cytochrome P450 2E1 genotype and haplotype in pediatric patients

To the Editor,

Previous reports have shown that polymorphisms in *NAT2* and *CYP450 2E1* genes contribute to antituberculosis drug (ATD)-induced hepatotoxicity in adults in different populations.[1–3] In the present study, the association between risk of hepatotoxicity and polymorphisms in these genes was examined in children.

The study involved 111 pediatric patients with tuberculosis (TB). Most of the patients were treated with isoniazid (INH; 5 mg/kg bodyweight per day), rifampicin (10 mg/kg bodyweight per day) and pyrazinamide (20–35 mg/kg bodyweight per day). A few patients with TB meningitis also received ethambutol (20 mg/kg bodyweight per day). After 2 months, pyrazinamide and ethambutol were discontinued and INH and rifampicin were continued for the next 4 months.

Of the 111 patients, nine showed symptoms of hepatotoxicity 1–6 weeks after commencing ATD treatment. One girl with hepatotoxicity had a positive test for hepatitis B virus surface antigen, so this patient was excluded from the study. The remaining 102 patients were considered non-toxic controls. However, subsequently during the course of treatment one non-toxic control was found to be infected with HIV, so this patient was also excluded from the study.

Therefore, eight of the total 109 (7%) pediatric patients with TB developed hepatotoxicity in this study (Table 1). Although children of both sexes had TB, all patients who developed hepatotoxicity were boys. The absence of any girls who developed hepatotoxicity in this study may indicate sex specificity for the development of ATD-induced hepatotoxicity in children, or it may be an effect of the small sample size. A report on Japanese pediatric patients also observed that more boys had hepatotoxicity than

Table 1 Characteristics of antituberculosis drug-induced hepatotoxic cases and non-toxic controls

Demographics and enzyme activity	Case ($n = 8$)	Control ($n = 101$)	*P*-value
No. patients			
Male	8	64	
Female	0	37	
Age (months)	53 ± 45 (11–144)	62 ± 39 (6–144)	0.48
ALT (IU/L)	364 ± 191 (97–540)	37 ± 16 (15–85)	<0.0001
AST (IU/L)	202 ± 142 (70–420)	32 ± 12 (13–67)	<0.0001
Bilirubin (mg/dL)	4.4 ± 3.0 (1.4–9.9)	0.7 ± 0.1 (0.5–0.9)	<0.0001
ALP (IU/L)	243 ± 233 (78–625)	95 ± 35 (39–207)	<0.0001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase. Normal values: ALT, 5–40 IU/L; AST, 5–40 IU/L; ALP, 60–170 IU/L; total bilirubin, 0.1–0.8 mg/dL.
Values shown as mean ± SD (range).

Table 2 Distributions of genotypes at *CYP2E1 DraI*, 96-bp *indel*, *PstI* and *RsaI* polymorphic sites among hepatotoxic cases ($n = 8$) and non-toxic controls ($n = 101$)

Polymorphic site	Genotype	Cases *n* (%)	Controls *n* (%)	Significance Odds ratio (95% CI)
DraI	*CC*	2 (25)	3 (3)	11.0 (1.02–110)
	CD + ***DD***	3 + 3 (75)	33 + 65 (97)	
	Frequency of *C* allele	0.44	0.19	$P = 0.046$
96-bp *indel*	*II*	2 (25)	3 (3)	11.0 (1.02–110)
	ID + *DD*	3 + 3 (75)	46 + 52 (97)	
	Frequency of *I* allele	0.44	0.26	$P = 0.2$
PstI and *RsaI*	*c1/c1*	7 (87)	99 (98)	7.1 (0.2–124)
	c1/c2 + *c2/c2*	1 + 0 (13)	2 + 0 (2)	

CC, variant genotype (i.e. having absence of *DraI* restriction enzyme site); *II*, variant (insertion) genotype (i.e. having insertion of 96 bp in the allele); *c2/c2*, variant genotype at *PstI* and *RsaI* sites; *c1* allele, *RsaI*[+].*PstI*[–] haplotype; *c2* allele, *RsaI*[–].*PstI*[+] haplotype; + and –, presence and absence of restriction sites, respectively.

girls;[4] however, this finding should be confirmed with a larger sample size.

Total bilirubin contents and activities of serum alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase (ALP) were significantly higher in hepatotoxic patients than in non-toxic controls ($P < 0.0001$). As cases and controls were similar in mean ages and treated with the same regimen of ATD, it is highly probable that hepatotoxicity was manifested in some patients due to genetic susceptibility.

N-acetyl transferase 2 (NAT2) is expressed predominantly in the liver and is involved in the generation of precursors of hepatotoxins (such as acetyl hydrazine) in INH hepatotoxicity. Polymorphisms at *KpnI*, *TaqI* and *BamHI* sites on the *NAT2* exon could modulate the activity of the NAT2 enzyme and hence increase the risk of hepatotoxicity. In slow acetylators, acetyl hydrazine might accumulate in the liver as a source of hepatotoxin, because conversion of monoacetyl to diacetyl hydrazine, which is probably non-toxic, is lower in these individuals. A few reports, based on *NAT2* genotyping, have also shown that slow acetylators are susceptible to ATD-induced hepatotoxicity in different adult populations.[1,2] However, in the present study, genotyping data revealed that the proportions of *NAT2* slow acetylators were similar in the hepatotoxic cases and in the non-toxic controls (63% and 56%, respectively). As the sample size was low, the effect of acetylation status on the risk of hepatotoxicity may not have been able to be observed in this study. In an Indian population, the majority of the controls were slow acetylators (56%), whereas the majority of controls were fast/rapid acetylators (90% and 78%, respectively) in Japanese and Taiwanese populations.[1,2] So, apart from low sample size, differences in age (adult *versus* children) and proportions of slow acetylators might have contributed to the differences in results obtained in this and other studies. Several phenotypic studies also demonstrated that the acetylation status of patients might not have a significant role in the development of ATD-induced hepatotoxicity.[5]

Acetyl hydrazine, one of the INH metabolites, could be oxidized by the CYP2E1 enzyme into ultimate hepatotoxins, such as acetyldiazene, ketene and acetylonium ion. Several studies have reported that the variant '*c2*', *C* and *I* alleles (at *PstI-RsaI*, *DraI* and 96 bp *indel* polymorphic sites, respectively) on *CYP2E1* are associated with enhanced enzyme activity. In this study, frequencies of variant *C/C* and *I/I* genotypes in hepatotoxic cases were significantly higher than non-toxic controls (OR = 11.0, 95% CI = 1.02–110; same value for both genotypes, Table 2). So, it can be interpreted that variant *C/C* and *I/I* genotypes could increase the production of hepatotoxins and hence the risk of hepatotoxicity. The frequency of *C* allele was over-represented in cases compared to controls ($P = 0.046$); however, those of *I* alleles were not significantly different in cases and controls ($P = 0.2$). Because alleles at *PstI* and *RsaI* sites are in strong linkage disequilibria, polymorphisms at these sites could be expressed as *c1* and *c2* alleles. The variant *c2/c2* genotype was absent in cases

and controls. Although 13% of cases and 2% of controls had the heterozygous *c1/c2* genotype, they were not significantly different. In Taiwanese adult hepatotoxic patients, the *c1/c1* genotype was over-represented;[3] however, this was not found in the present pediatric population. The differences in the frequencies of wild-type *c1* and variant *c2* alleles in different populations (0.76 and 0.24 in Taiwanese and 0.99 and 0.01 in Indian populations) might have contributed to this difference.

Although polymorphisms at *PstI* and *RsaI* sites did not increase the risk of hepatotoxicity, polymorphisms at *DraI* and *indel* sites on the same gene did increase the risk of hepatotoxicity. The *c1-I-C* and *c1-D-D* haplotypes, estimated from genotypes at *PstI-RsaI*, *indel* and *DraI* sites, were observed to be major haplotypes present in both cases and controls. However, the *c1-I-C* haplotype increased the risk of hepatotoxicity (OR = 4.6, 95% CI = 1.3–16.3, data not shown). This haplotype contains the variant *I* and *C* alleles and the wild-type *c1* allele, which also corroborate the result that showed *c1/c1* genotype increased the risk of hepatotoxicity.[3] Currently haplotype rather than genotype is considered as the functional unit in determining susceptibility to a disease. In this context, *c1-I-C* haplotype on *CYP2E1* could be a marker for ATD-induced hepatotoxicity. So, pathways of hepatotoxicity development in children (this study) and adults (in other studies) may have a commonality such as involvement of the *CYP2E1* gene.

In conclusion, this study found that variant genotypes (*C/C* and *I/I*) and haplotype (*c1-I-C*) on *CYP2E1* increased the risk of hepatotoxicity in pediatric patients. However, a study with larger sample sizes will provide a better basis on which to predict ATD-induced hepatotoxicity in different populations.

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