

by restoring endothelial cell function of the portal vein in patients. However, the present study suggests that L-arginine deficiency in LPI can cause impairment of portal circulation via a decrease in NO production.

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Association study of TNFSF15 polymorphisms in Japanese patients with inflammatory bowel disease

Tumour necrosis factor superfamily (TNFSF) 15 is a novel member of the TNFSF and its mRNA and protein expression is upregulated in inflammatory bowel disease (IBD), particularly in Crohn's disease (CD).^{1,2} Recently, Yamazaki *et al* performed a large scale case control study using single nucleotide polymorphism (SNP) markers and reported that polymorphisms in *TNFSF15* conferred susceptibility to CD in both Japanese and UK populations.³ They also suggested a potential association between a Caucasian ulcerative colitis (UC) cohort and *TNFSF15*, but this association was not studied in Japanese patients. To investigate this possible association between *TNFSF15* and Japanese UC, and to replicate this association with CD in Japanese, we performed a case control association study in Japanese patients with CD and UC.

We selected six SNPs—*tnfsf15_26*, *tnfsf15_28*, *tnfsf15_31*, *tnfsf15_33*, *tnfsf15_35*, *tnfsf15_36*—which were reported to show a strong association ($p < 10^{-10}$), and genotyped these six SNPs in 286 patients with CD, 263 patients with UC, and 277 healthy controls (HCs) by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. All patients and HCs were Japanese, and none had a family history of IBD.

We replicated all six SNPs that were significantly associated with the Japanese CD cohort (table 1). On the other hand, in contrast with Caucasians,³ none of the SNPs were associated with the Japanese UC cohort. Risk allele frequencies of *tnfsf15_35*, *tnfsf15_36*, and *tnfsf15_31* were higher in the CD group with anal lesions than in those without, but the associations were statistically weak ($p = 0.019$, 0.019 , and 0.037 , respectively). No significant differences were found in allele frequencies between the CD subgroups classified by age at diagnosis, location of disease, existence of fistula, stenosis, need for steroid therapy, and past history of surgical treatment, and also the UC subgroups classified by age at diagnosis, extent of disease, need for intensive intravenous steroid therapy, and need for surgical treatment.

In this study, we confirmed the findings of a previous report concerning a significant association between *TNFSF15* and CD. On the other hand, no evidence for an association with Japanese UC was observed, although a potential association with Caucasian UC was reported. It is generally accepted that UC and CD may share some susceptibility genes. Ethnic differences in genetic susceptibility may be explained by differences in the haplotypic background. Some *TNFSF15* polymorphisms identified in the Japanese were monomorphic or nearly monomorphic in the Caucasian population.³ Thus it seems likely that population specific patterns of haplotypes may contribute to differences in UC susceptibility.

Although a previous report described that *tnfsf15_28* showed the lowest p value and highest odds ratio among the SNPs in *TNFSF15*,³ our results showed that p values and odds ratios of *tnfsf15_36* and *tnfsf15_35* were similar to those of *tnfsf15_28*. Thus to identify the pathogenic SNP, a functional study is clearly needed. We analysed the transcription factor binding sites in the promoter region of *TNFSF15* by TFSEARCH⁴ and found that GATA-1, 2, and 3 possibly bind the *tnfsf15_35*-T allele while the GATA binding *cis* element is absent in the *tnfsf15_35*-C allele (risk associated). It is well known that GATA-3 promotes a Th2 mediated immunological state and suppresses expression of Th1 mediated cytokines.^{5,6} These findings have raised the possibility that GATA-3 may not bind the promoter region with the *tnfsf15_35*-C risk allele resulting in lack of suppression of *TNFSF15* expression. Consequently, over-expressed *TNFSF15* promotes a Th1 mediated immunological state and initiates or exacerbates the severity of CD. Although we do not have experimental evidence for this hypothesis, we intend to elucidate the functional significance in the future.

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Table 1 Allele frequencies of *TNFSF15*

SNP	dbSNP	Location	Allele1	Allele2	Frequency of allele2 (%) / OR / p value		
					HCs (n = 277)	CD (n = 286)	UC (n = 263)
<i>tnfsf15_36</i>	rs7848647	5'-flanking region	G	A	39.0	25.7 (OR = 1.85, $p = 1.84 \times 10^{-6}$)	36.3 (NS)
<i>tnfsf15_35</i>	rs6478109	5'-flanking region	C	T	39.0	25.7 (OR = 1.85, $p = 1.84 \times 10^{-6}$)	36.3 (NS)
<i>tnfsf15_33</i>	rs6478108	Intron 1	A	G	51.8	37.6 (OR = 1.78, $p = 1.60 \times 10^{-6}$)	52.3 (NS)
<i>tnfsf15_31</i>	rs4979462	Intron 1	A	G	39.5	26.2 (OR = 1.84, $p = 1.98 \times 10^{-6}$)	36.5 (NS)
<i>tnfsf15_28</i>	–	Intron 3	C	T	53.1	38.8 (OR = 1.78, $p = 1.58 \times 10^{-6}$)	52.3 (NS)
<i>tnfsf15_26</i>	rs3810936	Exon 4 (Val201Val)	G	A	40.3	26.9 (OR = 1.83, $p = 2.15 \times 10^{-6}$)	36.3 (NS)

SNP, single nucleotide polymorphism; HCs, healthy controls; CD, Crohn's disease; UC, ulcerative colitis; NS, no significant. OR, odds ratio.

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NOTICE

The XXXI Pan American Congress of Digestive Diseases: Global challenges in gastroenterology from the end of the world

This conference will be held in Santiago, Chile, on 11–14 November 2008.

EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 1422

An abdominal operation revealed a hard whitish tumour. The tumour involved that part of the small intestine (fig 2). On pathological examination it was diagnosed as a metastasis from a pleomorphic carcinoma of the lung (fig 3). Metastasis of lung carcinoma to the small intestine has been reported to be in the range 2.6–10.7% in autopsy studies.^{1,2} Some cases of small intestine metastasis showed various symptoms, such as obstruction, malabsorption, haemorrhage, and perforation. Berger *et al* reported that 0.5% of patients operated on for lung carcinoma developed symptomatic small intestine metastases.³ In this case, the shape of the small intestine metastasis was unusual. Cancer cells were substituted for normal cells all round the intestinal wall. Intestinal fluid passed through inside the tumour so that, although he had

slight abdominal pain after meals, he did not have obstruction. Fortunately, it did not perforate.

Careful examination for intra-abdominal lesions is needed after resection of primary lung carcinoma. If acute abdomen occurs in patients with a known history of lung carcinoma, gastrointestinal metastasis must be considered.

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Figure 2 The tumour. The small intestine was segmented by the tumour but intestinal juice passed through the lumen of the tumour.

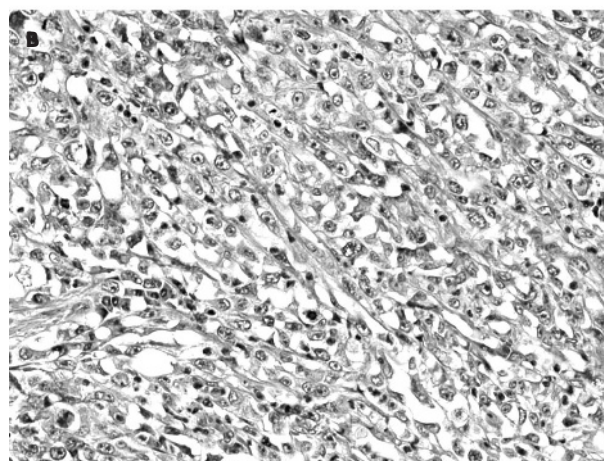
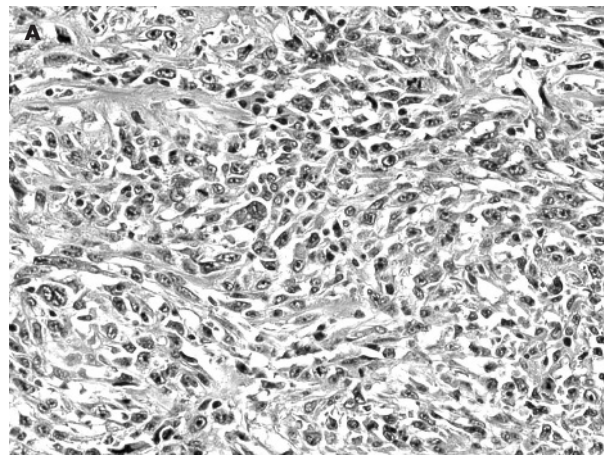


Figure 3 Pathological findings. On pathological examination, the structures of both the primary tumour (A) and metastatic tumour (B) were made of spindle cells and giant cell carcinoma. The similarity of the two tumours strongly supports the idea that the abdominal mass is a secondary.