

## Neuroleptic malignant syndrome versus malignant disease: idiosyncratic or synchronous?

Futoshi Shintani, Masaki Izumi, Naohiro Fujimura

*Lancet* 2009; 374: 90

Department of Psychiatry  
(F Shintani MD, N Fujimura MD),  
Department of Internal  
Medicine (M Izumi MD), Tokyo  
Musashino Hospital, Tokyo,  
173-0037 Japan

Correspondence to:  
Dr Futoshi Shintani, Tokyo  
Musashino Hospital,  
Komone 4-11-11, Itabashi-ku,  
Tokyo, 173-0037 Japan  
f-shintani@tmh.or.jp

In August, 2007, a 60-year-old man who had had bipolar disorder since 1990 was admitted to our hospital with recurrence of mania. Remission was achieved with lithium carbonate (400 mg/day) and zotepine (125 mg/day), and in November he was moved to an open ward. 1 week later we increased his lithium dose to 800 mg following relapse of mania. 4 days later, he developed a fever (39°C). He was alert, had pressure of speech, tachycardia, unstable blood pressure, and diaphoresis, but had no muscle rigidity. Blood test results showed mild anaemia, slight leucocytosis ( $9.6 \times 10^9/L$ ), high creatine kinase (CK, 330 U/L), slightly high aspartate transaminase (38 U/L) and alanine transaminase (33 U/L), and normal concentrations of thyroid hormones and electrolytes. CT of the head and chest radiography showed no foci of infection. Serum lithium concentration (0.57 mEq/L) was not suggestive of toxicity. We discontinued lithium, suspecting neuroleptic malignant syndrome from the rapidly increased dose 4 days earlier.

The next day, physical signs and white-cell count normalised, and 3 days later, CK concentration dropped to 210 U/L. However, CK isoenzyme MB rose to 103 U/L (normal <25 U/L) despite a negative cardiac troponin-T test. Electrocardiography and echocardiography showed no abnormalities. CK isoenzyme electrophoresis showed the presence of macro-CK type II, prompting us to search for malignancy. Faecal occult blood was positive, and our patient had high values of serum carcino-embryonic antigen (125 ng/mL; normal <5 ng/mL); an ulcerated tumour with infiltration 10 cm above the anal verge was seen on colonoscopy (figure A), which was identified as a well-differentiated adenocarcinoma on histopathological examination. Contrast-enhanced abdominal CT showed five low-density areas over 4 cm in diameter and seven smaller areas in the liver (figure B).

No metastases were seen elsewhere. Abdominal ultrasonography from March, 2007, had shown a normal liver without space-occupying lesions; of note, tests for faecal occult blood had been negative at the time of his current admission. Only upon inquiry did he disclose having had bloody stools since October. Our patient refused surgical intervention for his colorectal cancer, although he reluctantly consented to take doxifluridine (800 mg/day) and remained an in-patient. Although peritoneal carcinomatosis and extreme emaciation advanced, hypomanic episodes recurred. Our patient passed away in November, 2008.

Neuroleptic malignant syndrome is a rare but life-threatening complication of neuroleptic medications uncommonly induced by concomitant use of lithium or by sudden increase in dosages.<sup>1</sup> Common features include hyperthermia, rigidity, autonomic symptoms, and laboratory evidence of rhabdomyolysis.<sup>1</sup> Early detection and cessation of causative medicine are cardinal interventions for reducing mortality.<sup>1</sup> Our patient did not display signs of rigidity, but since not all symptoms appear simultaneously,<sup>1</sup> we provisionally diagnosed neuroleptic malignant syndrome and withdrew lithium. The finding of high concentration of macro-CK type II in his serum was suggestive of malignancy,<sup>2</sup> and colorectal cancer was detected. Colorectal cancer kills nearly 500 000 people each year worldwide, and liver metastases are found in approximately 20% at the time of diagnosis.<sup>3</sup> When treated with chemotherapy alone, most patients die within 2 years.<sup>3</sup> Bipolar patients have high rates (20–80%) of medical comorbidity<sup>4</sup> and distorted recognition of disease often delays diagnosis and therapy. High vigilance for medical illnesses is necessary when examining psychiatric patients.<sup>4</sup>

### Contributors

All authors participated in patient management; FS wrote the report.

### Acknowledgments

We thank M Yokota and S Eguchi for advice regarding patient management, and Y Kanai for commenting on the manuscript.

### References

- Hall RCW, Hall RCW, Chapman M. Neuroleptic malignant syndrome in the elderly: diagnostic criteria, incidence, risk factors, pathophysiology, and treatment. *Clin Geriatr* 2006; 14: 39–46.
- Stein W, Bohner J, Steinhart R, Eggstein M. Macro creatine kinase: determination and differentiation of two types by their activation energies. *Clin Chem* 1982; 28: 19–24.
- Poston GJ, Adam R, Alberts S, et al. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. *J Clin Oncol* 2005; 23: 7125–34.
- McLaren KD, Marangell LB. Special considerations in the treatment of patients with bipolar disorder and medical co-morbidities. *Ann Gen Hosp Psychiatry* 2004; 3: 7.

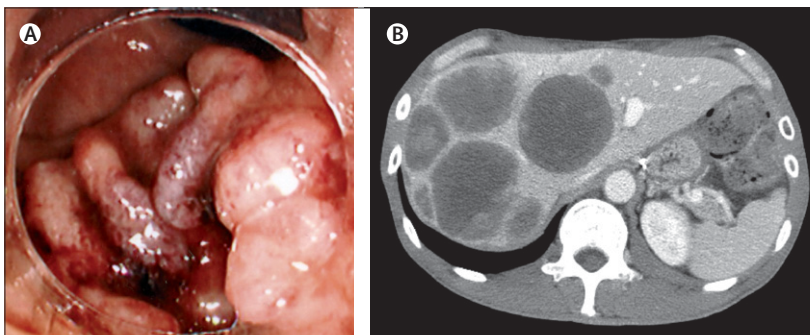


Figure: Synchronous rectal hepatic metastases (A) Flexible colonoscopy. (B) Contrast-enhanced CT.