

## Fluctuations in C-reactive protein in a hepatoblastoma patient with thrombocytosis

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### Abstract

We observed the changes in serum levels of interleukin 6 (IL-6) and C-reactive protein (CRP) in a patient with hepatoblastoma exhibiting thrombocytosis. The concomitant changes of IL-6 and CRP concentrations after the initiation of chemotherapy, in the absence of infection, suggested that the IL-6, which is synthesized in hepatoblastoma cells and induces thrombocytosis, also stimulated CRP production in the present case. IL-6 is thought to play an important role in thrombocytosis in hepatoblastoma.

### Introduction

Hepatoblastoma is a commonly in the same phrase primary liver tumor of childhood, and marked thrombocytosis is commonly observed in hepatoblastoma patients.<sup>1-4</sup> Interleukin 6 (IL-6), which stimulates inflammatory thrombocytosis via thrombopoietin, is also elevated in hepatoblastoma patients with thrombocytosis.<sup>2,4-7</sup> In this study, we examined a five-month-old girl with hepatoblastoma who also had thrombocytosis. We observed increases in her C-reactive protein (CRP) and IL-6, in the absence of infection, after chemotherapy. Therefore, we inferred that IL-6 induces both thrombocytosis and elevated CRP in hepatoblastoma patients.

### Case Report

A five-month-old girl was admitted to our hospital with abdominal distention. A physical examination revealed a solid mass (10×12 cm<sup>2</sup>) in her right upper abdominal quadrant. Her white blood cell (WBC) and platelet counts were 15.6×10<sup>9</sup>/L and 94.8×10<sup>9</sup>/L, respectively. Her serum liver enzymes were minimally ele-

vated and her CRP was 2.24 mg/dL (normal range: 0-0.3 mg/dL). Her  $\alpha$ -fetoprotein was markedly elevated at 4.0×10<sup>6</sup> ng/mL (normal range in five-month-old infants: 8-800 ng/mL). A pathology examination through hepatoblastoma of combined fetal and embryonal types. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed that a solid mass had developed in the right lobe of the liver. From these radiological examinations, her stage was diagnosed as PRETEXT III. Chemotherapy was administered according to the Japanese Study Group for Pediatric Liver Tumor Protocol 2 (JPLT-2) with the CITA regimen: cisplatin (80 mg/m<sup>2</sup>) on day 1 and tetrahydropyranil-adriamycin (30 mg/m<sup>2</sup>) on day 2. However, the calculated dose was reduced by 70% based on her age (less than one year old) at first diagnosis, according to the JPLT-2 protocol. Her general condition was good, but her CRP increased from 2.4 to 11.2 mg/dL on day 7 after chemotherapy (Table 1). Her WBC count and procalcitonin, which are known to be sensitive markers of bacterial infection, were not elevated. Although no bacteria were detected in her blood, urine, or throat cultures, iv antibiotics for seven days. Her CRP levels were not influenced by the administration of antibiotics. The patient's CRP dropped to 2.4 mg/dL after four weeks without antibiotics (Table 1). A 50%-reduced CITA regimen was then administered again, based on the JPLT-2 protocol for six-month-old patients, and we monitored her CRP and IL-6 levels. Her CRP was 2.4 mg/dL and IL-6 was 17.1 pg/mL (normal range: 1.0-4.0 pg/mL) before chemotherapy, and both increased to 7.9 mg/dL and 103.0 pg/mL, respectively, seven days after chemotherapy. CRP (1.1 mg/dL) and IL-6 (11.2 pg/mL) were restored after 28 days, without injected antibiotics (Table 1). After the complete surgery of hepatoblastoma, CITA was repeated 6 times, IL-6 was decreased to 1.6 pg/mL and both of CRP and platelet counts was kept in normal range.

### Discussion

Thrombocytosis was previously recognized as a common complication in hepatoblastoma patients.<sup>1-4</sup> Elevated serum IL-6 in hepatoblastoma patients with thrombocytosis was previously reported.<sup>2,4-7</sup> Therefore, IL-6, which is synthesized in hepatoblastoma cells, stimu-

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lates thrombocytosis via thrombopoietin.<sup>3,8</sup>

IL-6 also regulates the production of CRP at the transcriptional level in hepatocytes.<sup>9,10</sup> Fluctuations in CRP were observed in our patient and a low-grade elevation of CRP (less than 2.0 mg/dL) continued between her chemotherapy sessions. About one week after chemotherapy, her CRP had increased from the primary level to 10.5 mg/dL, with no symptoms of infection. The patient's level of procalcitonin, a marker of infection, and WBC count were within normal ranges. All bacterial cultures were also negative. The elevation of IL-6 followed the same ascending course with CRP concentration. This phenomenon indicates that IL-6 triggered the production of CRP in hepatocytes, similar to the production of thrombopoietin. The serum concentration of IL-6, which is released from damaged hepatoblastoma cells after chemotherapy, increased and up-regulated the expression of CRP. Serum IL-6, CRP and platelet count were normalized after JPLT-2 protocol was performed completely. We consider that the fluctuations in CRP without infection are high suggestive for hepatoblastoma. It is important to determine whether antibiotics are necessary in hepatoblastoma patients after chemotherapy. We believe that the changes in IL-6 levels paralleled the elevation of CRP in the serum of our hepatoblastoma patient. We conclude that IL-6 production was induced in the hepatoblastoma cells, as a result of the destruction of these cells during chemotherapy, the serum IL-6 concentration increased, causing an increase in serum CRP and thrombocytosis.

**Table 1. C-reactive protein and Interleukin-6 concentrations in a hepatoblastoma patient during chemotherapy.**

	Pre-treatment	Week 1	Week 4	Week 5	Week 9	Post-treatment
CRP (mg/dL)	2.4	11.2	2.4	7.9	1.1	0.2
IL-6 (pg/mL)	NA	NA	17.1	103.0	11.2	1.6

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## Conclusions

We reported the changes in serum levels of interleukin 6 (IL-6) and C-reactive protein (CRP) in a patient with hepatoblastoma exhibiting thrombocytosis. The elevation of IL-6 paralleled the increase in the serum CRP concentration.

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