INTERNAL MEDICINE

□ CASE REPORT □

Synchronous Occurrence of Diffuse Large B-cell Lymphoma of the Duodenum and Gastrointestinal Stromal Tumor of the Ileum in a Patient with Immune Thrombocytopenic Purpura

Tohru Takahashi [1], Yumiko Maruyama [1], Mayuko Saitoh [2], Hideto Itoh [2], Mitsuru Yoshimoto [2], Masayuki Tsujisaki [2] and Masato Nakayama [3]

Abstract

A 64 year-old woman with steroid-dependent immune thrombocytopenia developed anemia. Esophagogastroduodenoscopy revealed the presence of a tumor, which was diagnosed to be diffuse large B-cell lymphoma, in the second portion of the duodenum. ^{18}F-fluorodeoxy glucose positron emission tomography showed an increased uptake mass in the pelvic cavity as well as in the duodenum. Though the duodenal tumor disappeared after 4 cycles of chemotherapy, the pelvic mass did not shrink in size. As a result, laparoscopic resection of the pelvic tumor was performed and the tumor was histologically diagnosed to be a gastrointestinal stromal tumor. Subsequently, the patient was treated with 2 more cycles of the chemotherapy. Eventually, thrombocytopenia completely resolved.

Key words: lymphoma, GIST, ITP

(Intern Med 55: 2951-2956, 2016)
(DOI: 10.2169/internalmedicine.55.6712)

Introduction

Gastrointestinal stromal tumors (GISTs) are an uncommon mesenchymal neoplasm of the gastrointestinal (GI) tract. They occur most commonly in the stomach (60-70%), followed by the small intestine (20-30%). The synchronous occurrence of other malignancies in the patients with GIST during their clinical courses is relatively common (1, 2). However, the synchronous coexistence of GIST and GI lymphoma has only rarely been reported (3-8). We herein report a unique case of ileal GIST which was incidentally discovered during the course of chemotherapy for duodenal diffuse large B-cell lymphoma (DLBCL). The patient had also been diagnosed to have immune thrombocytopenic purpura (ITP) before the diagnosis of DLBCL was made.

Case Report

A 62-year-old woman was referred to us due to the onset of purpura and thrombocytopenia in April 2012. The white cell count was 4, 320/μL, the hemoglobin concentration was 11.3 g/dL, and the platelet count was 27,000/μL. Serum biochemistry tests were normal. Physical examination showed no abnormal findings except for quite a few purpura in the upper and lower extremities. A bone marrow examination revealed normocellular marrow without myelodysplasia, and a chromosomal analysis was normal. She was diagnosed to have ITP. Esophagogastroduodenoscopy (EGD) was performed and chronic gastritis was diagnosed. No tumors in the duodenum were observed at that time. A urea breath test was positive and a combination therapy with antibiotics (amoxicillin 750 mg twice daily and clarithromycin 200 mg twice daily for 7 days) and a proton pump inhibitor (esomeprazole 20 mg twice daily for 7 days) for the eradication of

[1]Department of Hematology, Tenshi Hospital, Japan, [2]Department of Gastroenterology, Tenshi Hospital, Japan and [3]Department of Surgery, Tenshi Hospital, Japan
Received for publication October 19, 2015; Accepted for publication March 1, 2016
Correspondence to Dr. Tohru Takahashi, tohrut@cocoa.ocn.ne.jp

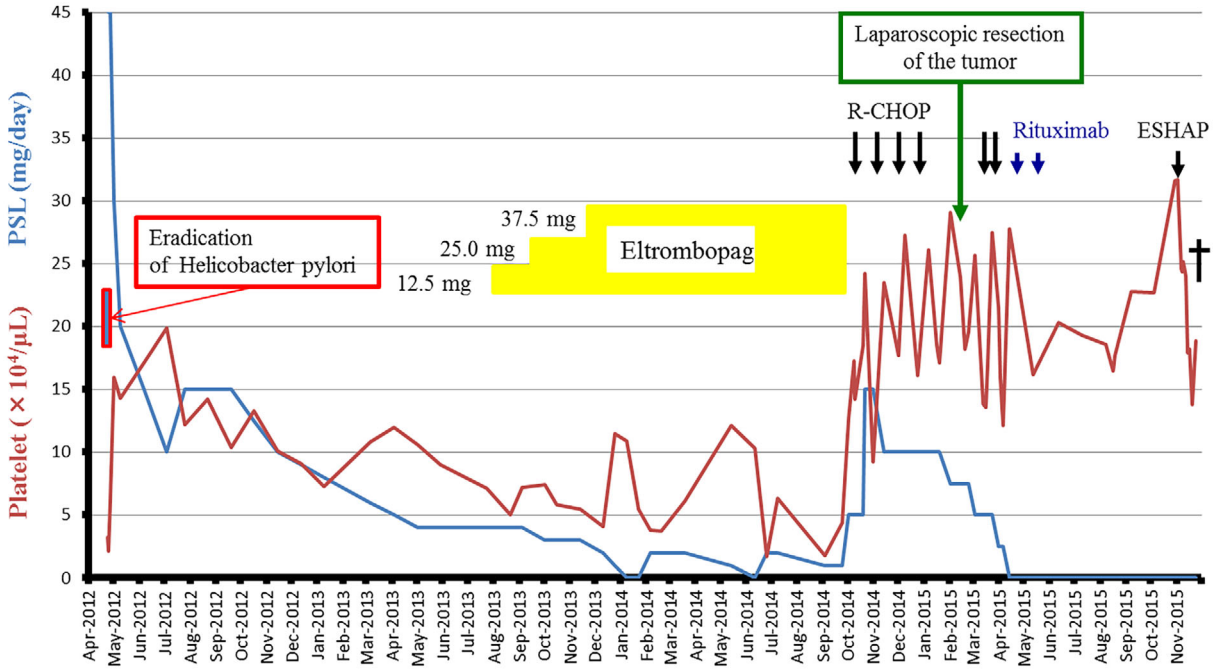

Figure 1. **Clinical course.**

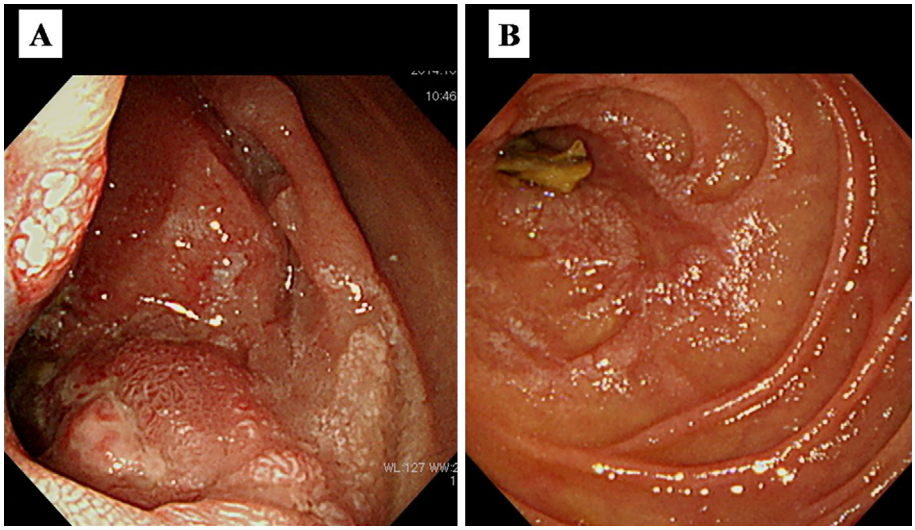

Figure 2. **Upper gastrointestinal endoscopic examination showed a circumferential ulcerating tumor mimicking a type II-like tumor in the second portion of the duodenum (A). The tumor disappeared after 4 cycles of R-CHOP therapy (B).**

the *Helicobacter pylori* (HP) was carried out. At the same time, she was started on prednisolone (1 mg/kg per day) because of worsening of the purpura and the platelet count decreased to 21,000/μL. Her platelet count thereafter quickly increased (Fig. 1). The urea breath test again carried out and the eradication of the HP was found to be successful. However, thrombocytopenia recurred when the steroid dosage was tapered. Because she refused to undergo splenectomy, eltrombopag was used with a small dose of prednisolone to maintain her platelet count. In the meantime, the patient developed mild iron deficiency anemia in October 2014 (at 64 years of age). Occult blood of feces was negative. EGD revealed a circumferential ulcerative tumor mimicking type 2 advanced cancer (Fig. 2A). A pathological examination of the biopsied specimen showed a diffuse infiltration of large lymphoid cells which were positive for CD20 but negative for CD3 (Fig. 3). A flow cytometric analysis showed the tumor cells to be positive for CD 19, 20 and lamda chain, but negative for CD3, 5, 10, 23 and kappa chain. As a result, a diagnosis of DLBCL was made. An ^{18}F-fluorodeoxy glucose (FDG) positron emission tomography (PET) study with a simultaneous whole body computed tomography (CT) scan showed a markedly increased uptake of FDG in the duodenum (Fig. 4A). An FDG-positive round mass in the right

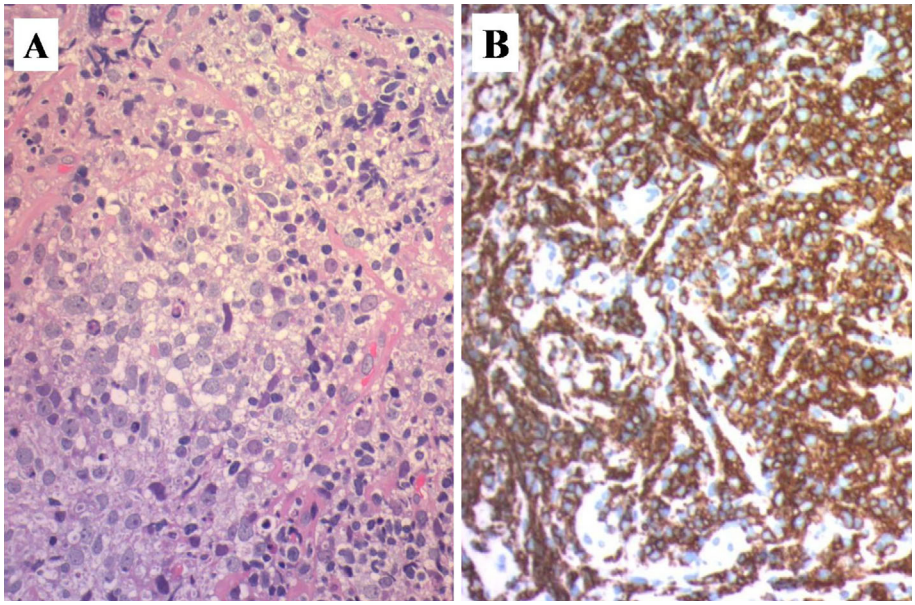

Figure 3. **A duodenal biopsy showed the diffuse infiltration of large lymphoid cells (Hematoxylin and Eosin staining) (A). The cells were positive for CD20 (B).**

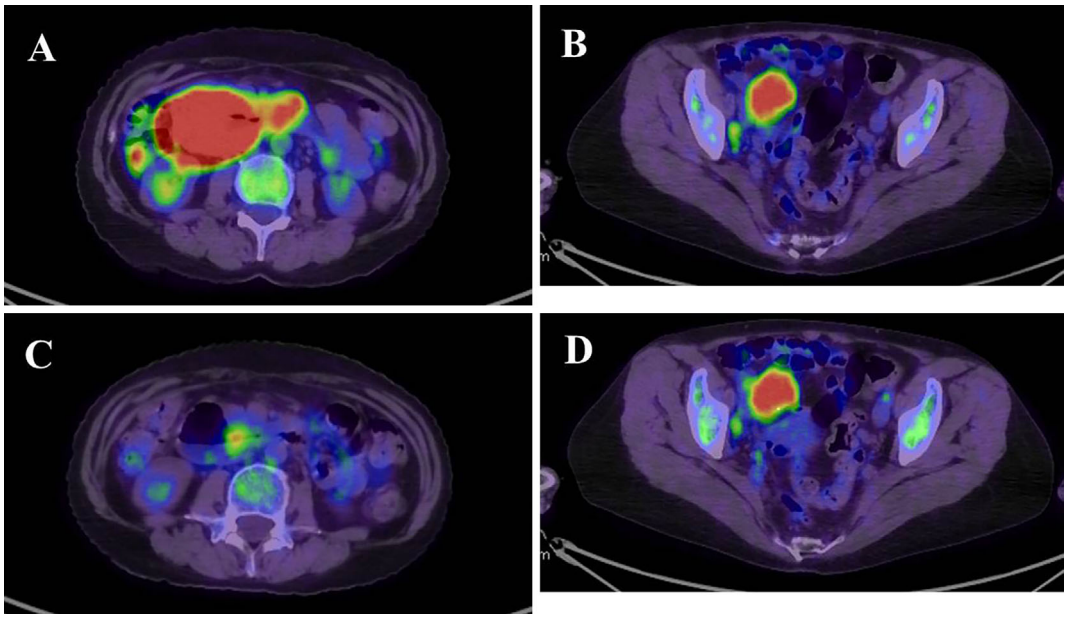

Figure 4. **FDG-PET/CT study showed a significant uptake in the duodenum (A) and the pelvic mass (B) before chemotherapy. After chemotherapy, the duodenum mass disappeared (C) while the pelvic mass remained (D).**

pelvic cavity was also found (Fig. 4B). Although the possibility of another malignancy could not be ruled out, the mass was considered to be an enlarged mesenteric lymph node that had been infiltrated by lymphoma cells at that time. She was treated with standard R-CHOP (consisted of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy. After the 4th cycle of the therapy, the duodenal tumor was not detected by EGD (Fig. 2B). An interim FDG-PET study showed that the mass in the pelvic cavity had not shrunk at all, while the duodenal lesion had completely disappeared (Fig. 4C and D). Laparoscopic resection of the tumor with its adjacent ileum was thereafter successfully carried out. The tumor was a well-demarcated capsulated mass measuring 5 cm in diameter and it protruded from the intestine to the peritoneal cavity (Fig. 5). A pathological examination disclosed a proliferation of spindle shaped cells with only slight mitotic activity (Fig. 6). An immunohisotochemical study showed the cells to be positive for CD117(c-KIT) and CD34, and the MIB-1 index was less than 1%. Thus, a diagnosis of GIST with an intermediate risk was made. The patient was treated with 2 more courses of R-CHOP therapy. The FDG-PET study on June 2015

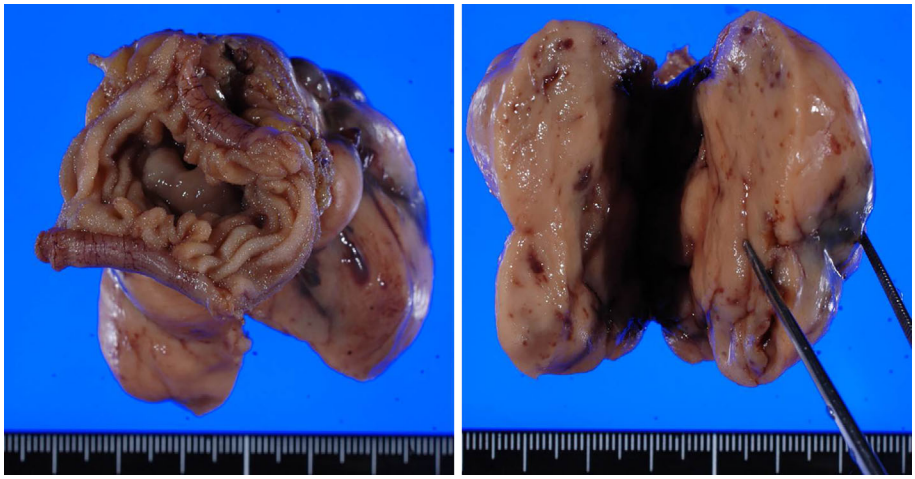

Figure 5. **A fixed resected specimen of the pelvic tumor. A well-demarcated mass measuring 5 cm in diameter is observed.**

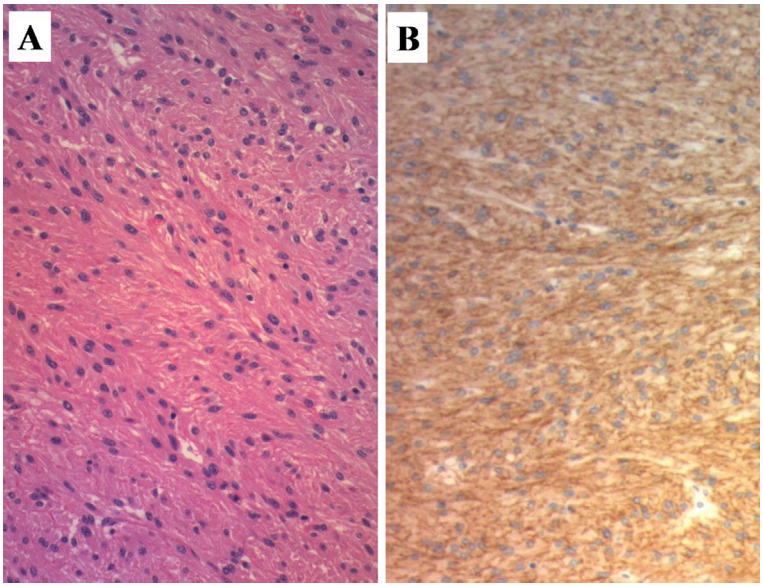

Figure 6. **A resected pelvic tumor contained spindle shaped cells (Hematoxylin and Eosin staining) (A). The cells were positive for CD117 (B).**

showed no abnormal uptake. Her platelet count had been normal without the administration of steroids or eltrombopag after the chemotherapy. However, lumbago and a pain in the right leg developed in October 2015. A CT scan of the abdomen showed a large mass (9.6×6.6×6.7 cm) in the right lower abdominal cavity. A percutaneous biopsy of the tumor revealed a recurrence of DLBCL. She was treated with ESHAP (consisted of etoposide, cisplatinum, high dose Ara-C, and methyl prednisolone) therapy without success and she died of the tumor progression in November 2015.

Discussion

The present patient was found to have duodenal DLBCL in her course of ITP. Autoimmune disorders are occasionally associated with lymphoid malignancies. ITP may occur in lymphoproliferative diseases, such as chronic lymphocytic leukemia (9), but it is rare in patients with malignant lymphoma. The prevalence of ITP in non-Hodgkin lymphomas has been reported to be less than 1% (10). Among these, DLBCL is extremely rare. To our knowledge, there have only been 7 reported cases of definitely diagnosed DLBCL associated with ITP in the English literature (Table 1) (11-17). Three cases were primary adrenal lymphomas and two cases were stage IV diseases involving extra nodal lesions (1 mesentery and 1 ascending colon, pancreas, and adrenal gland etc.). Three cases were refractory to steroid therapy (12, 14, 15). A complete resolution of thrombocytopenia was achieved in two cases after performing successful lymphoma therapies (15, 17) and in three cases after splenectomy (12, 13, 16). The pathogenesis of ITP associated with lymphoma is still not fully understood. In one case, the production of antiplatelet antibody from lymphoma cells was confirmed (14). However, the direct causative relationships

Table 1. Reported Cases of DLBCL Associated with Immune Thrombocytopenic Purpura.

Age / Sex	Origin of DLBCL	Treatment for DLBCL	Response	Thrombocytopenia	Reference
69/M	Mesentery	Surgery + chemotherapy	CR	Persisted	(11)
61/F	Adrenal glands	Surgery + chemotherapy	CR	Resolved by splenectomy	(12)
63/M	Adrenal glands	Surgery + chemotherapy	CR	Resolved by splenectomy	(13)
61/F	Adrenal glands	Chemotherapy	PR	Improved by chemotherapy	(14)
59/F	Colon	Chemotherapy	CR	Resolved by chemotherapy	(15)
51/M	Nodal	Chemotherapy	CR	Resolved by splenectomy	(16)
80/M	Nasopharynx + LN	Chemotherapy + RT	CR	Resolved by radiotherapy	(17)
64/F	Duodenum	Chemotherapy	CR	Resolved by splenectomy	Present case

DLBCL: diffuse large B-cell lymphoma, CR: complete remission, PR: partial remission, LN: lymph nodes, RT: radiotherapy

Table 2. Reported Cases of Simultaneous GIST and GI-lymphoma.

Age/Sex	Location of GIST	Location of lymphoma	Histology	Reference
77/F	Stomach	Stomach	DLBCL	(3)
78/M	Stomach	Stomach	MALT lymphoma	(4)
73/M	Stomach	Stomach	CLL type NHL	(5)
54/F	Stomach	Stomach	MALT lymphoma	(6)
68/M	Stomach	Stomach	Low grade BCL	(7)
65/F	Appendix	Ileocecal lesion	MCL	(8)
64/F	Ileum	Duodenum	DLBCL	Present case

GIST: gastrointestinal stromal tumor, MALT: mucosa associated lymphoid tissue, CLL: chronic lymphocytic leukemia, NHL: non-Hodgkin lymphoma, DLBCL: diffuse large B-cell lymphoma, MCL: mantle cell lymphoma

between ITP and DLBCLs could not be identified in the other reported cases. The present patient responded well to steroid therapy before undergoing chemotherapy, and thrombocytopenia completely resolved without either steroids or eltrombopag after the chemotherapy. Even after the recurrence of the lymphoma, the platelet counts remained normal. Therefore, it is not likely that the lymphoma cells produced autoantibodies to the platelet in the present case. Rituximab is reported to be effective for chronic ITP refractory to steroids or splenectomy (18). The patients treated with R-CHOP (15, 16, and the present case) showed a resolution of thrombocytopenia without steroids after the therapy. R-CHOP therapy may therefore provide sufficient immunosupression for ITP.

The patient was started on prednisolone immediately after admission because of severe purpura before *Helicobacter pylori* eradication therapy was started. It was reported that *Helicobacter pylori* eradication could induce platelet recovery in almost half of ITP patients (19). However, it took 2 to 3 months until the response was obtained. Thrombocytopenia recurred in the present patient when the steroids were tapered. Therefore, the eradication of *Helicobacter* was not considered to be effective in this case.

GIST is an uncommon neoplasm affecting the gastrointestinal tract. Though approximately 5% of GISTs have a hereditary etiology (20), most GISTs develop in a sporadic fashion and are usually located in the stomach and small intestine. The present patient had sporadic ileal GIST which was incidentally found in the course of duodenal DLBCL. The FDG-positive round mass in the right pelvic cavity was considered to be an enlarged mesenteric lymph node infiltrated by lymphoma cells at first because the tumor did not appear to develop from the intestine. We should have performed a biopsy before the R-CHOP therapy was started. Almost one-third of all reported GISTs are discovered incidentally during the investigative or therapeutic procedures for unrelated diseases. In addition, GI adenocarcinomas are the most prevalent GIST-associated cancers (47%) (1). Wronski et al. reported that 4 of 28 GIST patients (14%) simultaneously had other primary GI malignancies at their institution and they suggested the possible involvement of the same carcinogenic agents (3). There have only been 6 reported cases of concomitant GIST and GI lymphoma to date (Table 2). Three of these cases had gastric GISTs and gastric mucosa associated lymphoid tissue (MALT) lymphomas. To our knowledge, the cases of simultaneous occurrence of DLBCL and GIST in the small intestine have never been reported.

A recent population-based analysis has also confirmed many significant associations between GISTs and other cancers including non-Hodgkin lymphoma (2). Lymphoma patient may thus have higher tendency to have GIST, and vice versa. However, it is not clear whether these two tumors develop due to the same underlying etiology or not.

We herein reported a case of concurrent primary duodenal DLBCL and small intestinal GIST associated with ITP. Though the simultaneous occurrence of these diseases may be only coincidental, its clinical course was unique and interesting. We hope that this report will be of some use for the management of double cancer patients associated with autoimmune diseases such as ITP.

The authors state that they have no Conflict of Interest (COI).

References

1. Agaimy A, Wünsch PH, Sobin LH, Lasota J, Miettinen M. Occurrence of other malignancies in patients with gastrointestinal stromal tumors. Semin Diagn Pathol **23**: 120-129, 2006.
2. Murphy JD, Ma GL, Baumgartner JM, et al. Increased risk of additional cancers among patients with gastrointestinal stromal tumors: A population-based study. Cancer **121**: 2960-2967, 2015.
3. Wronski M, Ziarkiewicz-Wroblewska B, Gornicka B, et al. Synchronous occurrence of gastrointestinal stromal tumors and other primary gastrointestinal neoplasms. World J Gastroenterol **12**: 5360-5362, 2006.
4. Kaffes A, Hughes L, Hollinshead J, Katelaris P. Synchronous primary adenocarcinoma, mucosa-associated lymphoid tissue lymphoma and a stromal tumor in a *Helicobacter pylori*-infected stomach. J Gastroenterol Hepatol **17**: 1033-1036, 2002.
5. Herbers AH, Keuning JJ. Staging for CLL-type non-Hodgkin's lymphoma reveals a gastrointestinal stromal tumour. Neth J Med **63**: 74-75, 2005.
6. Salar A, Ramón JM, Barranco C, et al. Double diagnosis in cancer patients and cutaneous reaction related to gemcitabine: CASE 1. Synchronous mucosa-associated lymphoid tissue lymphoma and gastrointestinal stromal tumors of the stomach. J Clin Oncol **23**: 7221-7223, 2005.
7. Pamukçuoglu M, Budakoğlu B, Han O, et al. An extraordinary case in whom gastrointestinal stromal tumor and low-grade malignant lymphoma are seen together in the stomach. Med Oncol **24**: 351-353, 2007.
8. Rahimi K, Gologan A, Haliotis T, Lamoureux E, Chetty R. Gastrointestinal stromal tumor with autonomic nerve differentiation and coexistent mantle cell lymphoma involving the appendix. Int J Clin Exp Pathol **2**: 608-613, 2008.
9. Kaden BR, Rosse WF, Hauch TW. Immune thrombocytopenia in lymphoproliferative diseases. Blood **53**: 545-551, 1979.
10. Hauswirth AW, Skrabs C, Schützinger C, et al. Autoimmune thrombocytopenia in non-Hodgkin's lymphomas. Haematologica **93**: 447-450, 2008.
11. Moriwaki Y, Naka M, Yamamoto T, et al. Malignant lymphoma in the mesentery with immune thrombocytopenia. Intern Med **31**: 1185-1189, 1992.
12. Baudard M, Pagnoux C, Audouin J, et al. Idiopathic thrombocytopenic purpura as the presenting feature of a primary bilateral adrenal non Hodgkin's lymphoma. Leuk Lymphoma **26**: 609-613, 1997.
13. Yamamoto E, Ozaki N, Nakagawa M, Kimoto M. Primary bilateral adrenal lymphoma associated with idiopathic thrombocytopenic purpura. Leuk Lymphoma **35**: 403-408, 1999.
14. Nobuoka A, Sakamaki S, Kogawa K, et al. A case of malignant lymphoma producing autoantibody against platelet glycoprotein Ib. Int J Hematol **70**: 200-206, 1999.
15. Uchiyama M, Sato K, Ikeda T. Diffuse large B-cell lymphoma complicated with autoimmune thrombocytopenia. Intern Med **50**: 1215-1218, 2011.
16. Park SY, Kim S, Kim ES, et al. A case of non-Hodgkin's lymphoma in patient with Coombs' negative hemolytic anemia and idiopathic thrombocytopenic purpura. Cancer Res Treat **44**: 69-72, 2012.
17. Berrang T, Holloway C, Hart J, Yee A, Berry B, Kotb R. Successful treatment of non-Hodgkin lymphoma associated immune thrombocytopenia with involved field radiotherapy. Hematol Oncol **31**: 218-220, 2013.
18. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood **98**: 952-957, 2001.
19. Emilia G, Longo G, Luppi M, et al. *Helicobacter pylori* eradication can induce platelet recovery in idiopathic thrombocytopenic purpura. Blood **97**: 812-814, 2001.
20. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer **103**: 821-829, 2005.