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LETTERS AND CORRESPONDENCE

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Primary Granulocytic Sarcoma of the Nasopharynx

To the Editor: Granulocytic sarcomas (GS) or chloromas are solid masses of myeloid leukemia cells. The most common sites include the female reproductive tract, breast, skin, gut, and testis [1]. Most cases are secondary to systemic leukemia or represent disease progression in acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or chronic myeloid leukemia (CML). An increasing incidence of GS has also been observed after allogeneic bone marrow transplantation for AML and CML [2]. Primary GS is a rare disease and can cause diagnostic pitfalls, especially for disease at uncommon sites and without concomitant marrow involvement. We present the first case of isolated primary GS in the nasopharynx (NP).

A 37-year-old Chinese man presented with serous otitis media of the right ear and myringotomy and grommet insertion was performed. Random nasopharynx (NP) biopsies for suspected nasopharyngeal carcinoma (NPC) showed only nonspecific inflammation. Two months later, he presented again with blood-stained post-nasal drip and left ear conductive deafness. A magnetic resonance imaging (MRI) showed NP infiltration (Fig. 1a), with no other lesions in the thorax, abdomen, or pelvis. A repeat examination showed inflamed and irregular mucosa. A biopsy showed submucosal invasion by sheets of myeloid blast cells (Fig. 1b), positive for CD45 and myeloperoxidase and negative for CD20 and CD3. The blasts did not express CD56, a natural killer cell marker associated with GS. A bone marrow biopsy was normal and molecular testing for the AML1/ETO gene fusion was negative (data not shown). Examination of the cerebrospinal fluid (CSF) was normal. He was treated as standard risk AML, with 7+3 induction chemotherapy [cytosine arabinoside (Ara-C) 100 mg/m^2 × 7, daunorubicin 50 mg/m^2 × 3], and consolidation [Ara-C 12 g/m^2 × 4 then 5+1 chemotherapy × 4 (Ara-C 100 mg/m^2 × 5, daunorubicin 50 mg/m^2 × 1)]. Radiotherapy (36Gy) was delivered to the NP. At three years, his marrow biopsy, computerized tomogram (CT) scan, and random NP biopsy were all normal.

The case illustrated some interesting features of GS. Firstly, GS involvement of the ear, nose, and throat area occurs occasionally, although almost all reported cases were accompanied by marrow disease [1]. Involvement of the upper aero-digestive area was observed in 3/24 cases of primary GS, and 2/34 cases of secondary GS post-BMT in two series [1,2]. Secondly, in Oriental patients, the NP is uniquely involved by a variety of neoplasms, especially NPC and T/NK cell lymphomas [3]. Rare hematolymphoid lesions such as Castleman's disease [4] and follicular dendritic cell sarcoma [5] also uniquely occur in the NP region in Oriental people. The recognition of GS from these other lesions is of clinical importance. It is not uncommon for GS to be misdiagnosed as lymphoma, and the poor clinical outcome of primary GS is partly due to inappropriate first-line therapy [1].

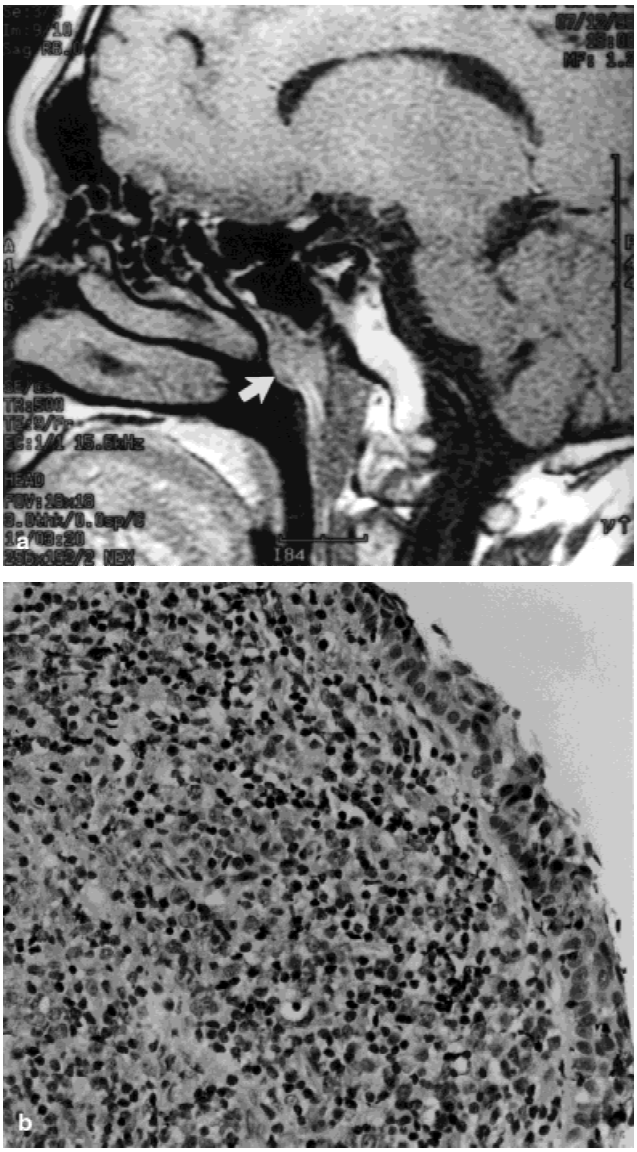

Fig. 1. (a) Sagittal MRI scan of the nasopharyngeal area showing localized thickening (arrow). (b) Biopsy showing sheets of leukemic blasts in the submucosa (H and E, original magnification ×250).

Myeloid GS will respond initially to RT and chemotherapy for NPC or NHL but will relapse as AML. At relapse, the disease is often refractory, compromising the overall cure rate. Thirdly, since synchronous or metachronous GS are common, radiological screening and consolidation RT are needed at diagnosis and follow-up to avoid local recurrence. Finally, due to the proximity of the NP area to the central nervous system, CSF involvement has to be excluded.

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Masked Deficit of B_{12} and Folic Acid in Thalassemia

To the Editor: The β-thalassemias are widespread throughout the world [1]. Macrocytosis, the hallmark of uncomplicated megaloblastic anemia, may be absent in individuals with either α- or β-thalassemia [2]. Its absence has been described in thalassemic subjects with nutritive deficiency of folate, vitamin B_{12}, or with co-existent pernicious anemia [2]. Anemia of varying degree is a quite common finding in thalassemia [3]. Frequently this anemia is related to hemoglobinopathies, but its occurrence in thalassemic patients who developed folic acid or vitamin B_{12} deficiency is usually unknown [4,5]. In nine patients of 20 with diagnosis of thalassemia evaluated in the last year, anemia is related to folic acid and B_{12} deficit. The laboratory data for these patients are given in Table I.

These clinical observations may remind us of microcytosis masking folate or vitamin B_{12} deficit. Moreover, in thalassemic heterozygotes who develop anemia, the possibility of megaloblastic pathogenesis should be pursued even when the RBC indices maintain their microcytic–hypochromic expression [3]. Because there are few reports in the literature describing megaloblastic anemia due to iatrogenic folate deficiency, we now prescribe drugs that interact with folate absorption or metabolism with caution and after frequent haematological controls in β-thalassemia heterozygous patients [5]. In addition, patients 3, 5, and 7 of the table, with chronic renal failure and microcytosis, did not respond to erythropoietin treatment for folic acid deficit. All of these observations suggest that thalassemic patients routinely need folic acid and vitamin B_{12} plasma assay, in order to prevent heavy anemia and to start correct therapy.

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Secondary Myelodysplastic Syndrome After Treatment of Prostate Cancer With Oral Estramustine

To the Editor: Katato et al. reported a patient with etoposide-associated secondary acute myelogenous leukemia (AML) in prostate cancer after treatment with oral etoposide and oral estramustine [1]. This patient received pelvic irradiation of 4,000 cGy and was treated with oral etoposide 50 mg/m^2/day and estramustine 10–15 mg/kg/day for 3 weeks, repeated every 4 weeks. He received 17 courses of treatment. He developed AML

TABLE I.

Patient no., age (years), sex	Thalassemia diagnosis	Hgb g/dl (12.0–16.0)	MCV fl (80–98)	Retycul. % (1–3)	B_{12} pg/ml (243–894)	Folic Acid ng/ml (4.2–19.9)
1/43/M	α	4.2	72.9	1	187	1.37
2/58/M	β	7.8	61.3	1.5	232	1.9
3/90/F	β	8.4	66	0.5	235	1.4
4/40/F	α	7.9	66	1.5	235	1.0
5/76/F	β	9.2	67	2.6	500	2.6
6/72/F	β	9.5	64	0.8	88	0.6
7/37/F	β	7.5	65.2	1.4	726	2.8
8/20/M	β	9.5	63	1.8	277	4.0
9/23/F	β	9.6	72.4	1.0	395	1.6

18 months after initiation of treatment with oral etoposide and estramustine for hormone-refractory prostate cancer and 3.5 years after pelvic irradiation of 4,000 cGy. A bone marrow biopsy revealed AML (subtype: M2) with dysplastic changes in all cell lines. Cytogenetic examination revealed 46, XY, t(8;21)(q22;22). Katato et al., however, speculated that oral etoposide rather than estramustine caused the secondary leukemia because secondary leukemia reported after the use of alkylating agents occurs after an average interval of 5–7 years. We encountered a patient who presented myelodysplastic syndrome (MDS) early after treatment with oral estramustine alone.

A 66-year-old man was diagnosed as having clinical stage C poorly differentiated adenocarcinoma of the prostate in November 1997. He was initially managed with leuprorelin acetate, a LH-RH agonist, once a month over one year. He then received chlormadinone acetate, a progesterone, until April 1999. He was treated with oral estramustine 560 mg/day, starting in May 1999, for 4 months. Thereafter, he received diethylstilbestrol, an estrogen, over 6 months, and subsequently bicalutamide, an antiandrogen, for 3 months. The laboratory data revealed a gradual progression of anemia and thrombocytopenia since April 2000. He received pelvic irradiation (6,000 cGy) since late June 2000. In July 2000, he was noted to have pancytopenia with circulating blasts. A bone marrow examination revealed MDS (subtype: refractory anemia with excess of blasts) with marked dysplastic changes in erythroid series. Cytogenetic examination showed a complex pseudodiploid with a stemline karyotype of 47, XY, −5, −5, −7, add(8)(p21), der(9)t(5;9)(q13;q14), +19, −20, +mar1, +mar2, +mar3, +mar4[cp].

Our patient received estramustine alone as an alkylating agent. Estramustine is a phosphorylated combination of estradiol and mechlorethamine (nitrogen mustard) [2]. It brings about disassembly of microtubles, leading to a disorientation of chromosomes in metaphase and consequently cell death. Furthermore, it inhibits assembly of microtubles. The compound binds to the so-called microtuble-associated proteins, which are essential for microtuble stability. Due to its microtuble-inhibiting activity, estramustine counteracts the invasive potential of hormone-refractory prostate cancer cells [3].

Our patient received not only an alkylating agent but also radiation therapy. Although radiation alone has the potential of leukemogenesis, it is unlikely that radiation therapy induced the secondary myelodysplastic syndrome, since his anemia and thrombocytopenia developed before radiation therapy. Secondary leukemia/myelodysplastic syndrome due to alkylating agents involves the most common numerical cytogenetic abnormalities of chromosomes 5 and 7, as with our patient [4].

Oral estramustine is widely used for hormone-refractory prostate cancer. It is important to emphasize the risk of secondary leukemias early after treatment with estramustine and subsequent radiation therapy.

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Effect of Pregnancy on Isolated Platelet Factor 3 (PF3) Defect

To the Editor: Isolated platelet factor 3 (PF3) availability defect is an uncommon but well-recognised hereditary bleeding disorder characterized by episodic bleeding since childhood [1–3]. There is no information in the literature, however, on the effect of pregnancy or the management of afflicted women during the perinatal period. This report describes two women with familial PF3 availability defect, in whom we have documented normal PF3 availability during pregnancy; both had normal, uncomplicated vaginal deliveries, without any precautions.

CASE 1

SG, a 22-year-old female, presented with a life-long history of mild spontaneous bruising and a significant family history (grandfather, father, paternal aunt, and brother) of bleeding tendency due to PF3 availability defect. Her grandfather and father have had major post-operative bleeding following surgeries (performed without prophylactic platelet transfusions), requiring blood transfusions. Her platelet count was normal (311×10^9/l), as were the in vitro platelet aggregation studies [4]; her skin bleeding time was prolonged at 12 min (NR 2–7.5 min) and the PF3 availability test [5] was abnormal.

She was reviewed 5 years after initial presentation, when she was 24 weeks pregnant. Repeat studies showed normal PF3 availability. She was allowed to deliver normally without platelet cover; there were no bleeding problems. Two years later, repeat studies showed PF3 availability defect.

CASE 2

SS, a 23-year-old female, presented in 1993 with a history of mild to moderate bruising since childhood; family history was non-contributory. At presentation, the platelet count was 253×10^9/l; skin bleeding time was prolonged at 9.5 min (NR 2–7.5); in vitro platelet aggregation studies were normal, but PF3 availability was abnormal. Six years later, she became pregnant and a repeat study showed normal PF3 availability. She subsequently had a normal vaginal delivery without any precautionary measures.

Isolated PF3 availability defect is due to a decreased ability to generate microparticles and decreased platelet membrane exposure of phosphatidylserine [2]. A recent report has documented improved PF3 availability in 35% of patients treated with soya bean [3], but platelet transfusion remains as the main form of treatment. To the best of our knowledge, normalisation of PF3 availability during pregnancy has not been reported previously. Saxena et al. [3] hypothesised a role for soya bean as a source of phospholipid, but the beneficial effect of pregnancy raises other possibilities, such as estrogen-mediated changes in the platelet membrane: soya bean is a rich source of phytoestrogens. Whatever the mechanism, our experience should negate the need for prophylactic platelet transfusions during the perinatal period.

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Near-Haploidy in Myeloid Antigen Positive Childhood Acute Lymphoblastic Leukemia

To the Editor: DNA ploidy of the leukemic blasts is an independent prognostic marker in childhood acute lymphoblastic leukemia (ALL) [1]. An uncommon hypodiploid karyotypic abnormality is near-haploidy [2]. Patients with near-haploid DNA usually have a poor prognosis in spite of a favorable immunophenotype (CD10 positivity) [3]. We describe here a case of childhood ALL with near-haploid DNA content and co-expression of CD10 and a myeloid antigen (CD13) by the lymphoblasts.

PA, a 14-year-old girl, presented with anemia, lymphadenopathy, easy bruisability, and fever. The total white cell count was 60×10^9/l. Both the peripheral blood and bone marrow showed an excess (>90%) of small lymphoblasts (FAB-L1). Both myeloperoxidase and Sudan Black B were negative. The blast cells showed reactivity with antibodies against CD10, CD19, CD22, and HLA-DR, thus confirming the diagnosis of precursor B-ALL. Additionally, over 60% of the blast cells showed expression of a myeloid antigen (CD13). The patient was treated with a modified BFM (Berlin, Frankfurt, Munich) protocol [4]. She has completed induction therapy and cranial irradiation and is in bone marrow remission at present.

The predominant clone of leukemic cells showed a near-haploid DNA index (DI = 0.56) represented by a single peak in the DNA histogram (Fig. 1). There was no obvious hyperdiploid clone derived from the near-haploid population. The synthetic (S)-phase fraction was 4.25%.

A near-haploid DI indicates a numeric chromosomal abnormality which reduces the number of chromosomes to nearly half of the normal. This rare abnormality is encountered most commonly in CD10-positive childhood ALL and predicts a poor prognosis in an otherwise favorable ALL subtype [2,3]. Childhood near-haploid ALL has been found to be associated with female sex, older age, high leukocyte count, and CD10-positive lymphoblasts, features shared by the patient described here. Interestingly, the blast cells in this patient were additionally CD13-positive, a feature not highlighted in the cases reported earlier [2,3].

Most of the cases of ALL with near-haploid DNA index described earlier had a morphologically distinct population of hyperdiploid clone arising by endoreduplication of the near-haploid line and having DI twice that of the near-haploid population [2,3,5]. Our patient had only one population of leukemic cells on DNA analysis representing the near-haploid lymphoblasts (Fig. 1). Because cytogenic study was not carried out in our case, it is possible that the G2/M peak of the near-haploid clone masked the presence of a minor hyperdiploid line in the DNA histogram. In some of the earlier reports, minor hyperdiploid clones could be identified by cytogenetic studies [2]. However, the presence or absence of a hyperdiploid line was not found to influence the prognosis in these cases [2,3,5].

The influence of near-haploidy of DNA and the expression of CD13 by the blast cells on the treatment outcome are yet to be manifested in this patient since she was in remission at the time of preparation of this letter. As reported in the earlier cases of near-haploid ALL, this patient also achieved bone marrow remission at the end of induction therapy [3].

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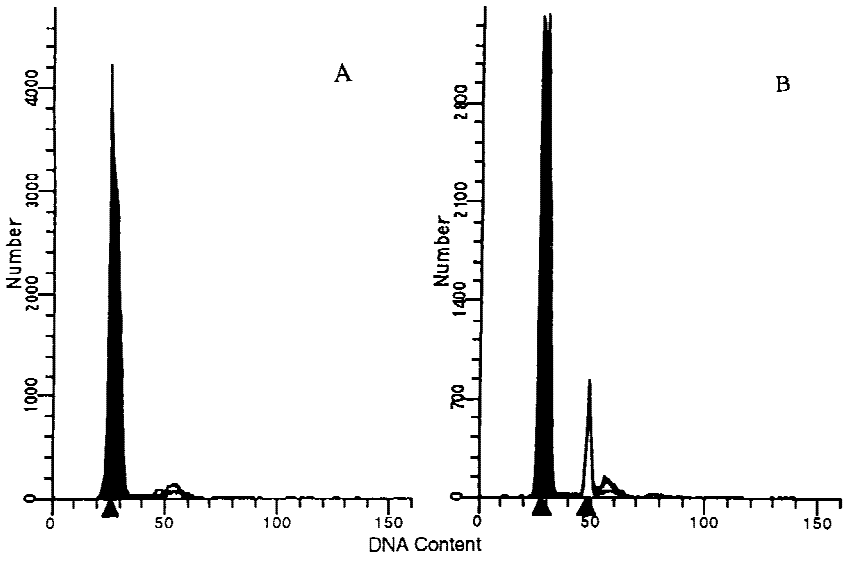

Fig. 1. DNA histograms of the patient's blast cells (A) and of the mixture of patient's cells with normal peripheral blood mononuclear cells (B) showing the near-haploid DNA index of the patient's cells. Note the absence of a significant hyperdiploid clone in the patient (A).

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Simvastatin-Induced Thrombocytopenia

To the Editor: The reductase inhibitors of the "statin" group of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) are frequently prescribed drugs, as clinical trials have demonstrated the benefits in reducing the cardiovascular-related mortality and morbidity in patients with hypercholesterolemia and mixed dyslipidaemia [1].

The most common adverse effects of the statins are headache, abdominal pain, constipation, diarrhea, and myalgia [2]. Recently, hematological disorders such as simvastatin-induced thrombotic thrombocytopenic purpura (TTP) [3] and severe thrombocytopenic purpura caused by atorvastatin [4] and simvastatin [5] have been reported. Unfortunately, these reports are not the only experiences of haematological disorders associated with the use of HMG-CoA reductase inhibitors. We present a patient who developed isolated thrombocytopenia while on simvastatin.

A 77-year-old woman was referred to the department of haematology with an isolated thrombocytopenia with a platelet count of 12×10^9/l. White blood count, hemoglobin, erythrocyte sedimentation rate, coagulation and liver function screens, electrolytes, and autoimmune screens were within normal limits. A peripheral blood smear and repeated platelet counts excluded pseudothrombocytopenia. Bone-marrow biopsy and aspirate showed a normal number and morphology of megakaryocytes as well as normal myelopoiesis and erythropoiesis.

On direct questioning the patient admitted to have easy bruising and occasional episodes of epistaxis since a few months. On examination there were no signs of petechiae or retinal hemorrhages and no splenomegaly.

She was started on treatment for hypercholesterinemia with 10 mg simvastatin (Zocor, Merck, Dohme, Whitehouse Station, NJ, USA) daily 11 months ago. She also gave a history of hypertension, treated with diltiazem 120 mg twice daily for 4 years, and a non-insulin dependent diabetes mellitus known for 7 years and well controlled with insulin.

As simvastatin was the last drug she was started on and closest to the beginning of episodes of epistaxis, it was discontinued. The platelet count rose to 83×10^9/l one week later and was within the normal range 3 weeks later. There were no further episodes of epistaxis and bruising.

The clinical course and the rapid improvement of the platelet counts after discontinuation of simvastatin observed in this case are highly suggestive of a simvastatin-induced immune thrombocytopenia.

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Flow Cytometric Analysis of an Expansion Paroxysmal Nocturnal Hemoglobinuria (PNH) Clone in a Patient With Bone Marrow Failure

To the Editor: We communicate our interesting studies made during the first haemolytic crisis from a patient diagnosed with aplastic anaemia (AA), and we show an evident expansion PNH clone in a few days. There was a great correlation between these results and the changes in the haematological parameters.

Although there are many reviews about diagnosis of PNH by flow cytometry and its relation with AA, there is no documentation of the expansion of the PNH clone during haemolytic crisis.

AA and PNH could be two different disorders [1] with the same basic defect. A high proportion of patients with AA are at risk for subsequently developing PNH clones during the evolution of the disease, especially if they are treated with immunosuppressive therapy [1,2]. PNH is an acquired clonal and haemolytic disorder characterized by the increased susceptibility of erythrocytes to complement-mediated haemolysis. Somatic mutations that affect the PIG-A gene [3] result in deficient synthesis of glycosyl phosphatidylinositol (GPI) [4]. The partial or complete lack of GPI-linked proteins on PNH cells plays a causative role in its pathogenesis.

A 27-year-old Caucasian female of European origin with previous history of anaemia was referred to our Institute. She showed ecchymosis and pallor. No organomegaly was found. Laboratory findings: RBC, 1.2×10^{12}/l; Hb, 3.7 g/dl, Hto, 0.1 l/l; reticulocytes, 19.2×10^9/l; WBC, 2.4×10^9/l; platelets, 25×10^9/l; total bilirubin, 6.84 μmol/l; serum iron, 410 mg/dl; transferrin saturation, 82%; HAM and sucrose tests—negative; viral antibodies—negative. Microscopic and cytogenetic bone marrow investigations, erythrokinetic studies, and reduced erythroid colony growth confirmed the diagnosis of AA. After 18 years of evolution, she showed clinical manifestations of dark urine and abdominal pain. At that moment (day 0), we evaluated CD59 on erythrocytes by flow cytometry [5,6]. CD59 staining clearly detected two red cell populations: PNH I cells with positive fluorescence like the normal and PNH III-negative cells. These affected cells increased on day 24 (Table I). Likewise, we analysed haematological parameters. HAM and sucrose tests were positive. Low Hb levels and erythrocyte counts were present, which continued decreasing on days 7 and 24 (Table I). High LDH levels (2350 UI/l), indirect bilirubin (42.4 μmol/l), and reticulocyte count were found. We established a good correlation among the clinical observations, the evolution of the laboratory parameters, and the expansion of the PNH clone evaluated by CD59 analysis. Other GPI-membrane erythrocytes (CD55) and leukocyte proteins (CD16 and CD14) were also decreased or absent. Also, leukocytes and neutrophils were decreasing during the follow-up haemolytic crisis (data not shown). The study was performed until day 24, when blood transfusion was required and the patient died after an infectious episode.

There is no clear explanation of the responsible causes of this haemolytic episode. It could be induced as a consequence of some mechanism that produced complement activation, such as a subclinical viral or bacterial infection. Increased compensatory rates of erythropoiesis (high levels of

TABLE I.

Day	RBC ($\times 10^{12}$/l)	Hb (g/dl)	PCV (l/l)	MCV (fl)	Retics ($\times 10^{9}$/l)	Eb (%)	CD59 PNH I cells (%)	CD59 PNH III cells (%)
0	3.28	9.8	0.31	94	272.2	2	48.3	51.7
7	2.72	8.3	0.26	96	279.7	27	48.2	51.8
24	2.29	7.5	0.23	100	274.8	35	29.6	70.4

reticulocytes and erythroblasts, LDH, and bilirubin in our case) might have led to the expansion of the PNH clone.

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Thalassemia Trait or Thalassemia Intermedia

To the Editor: I have read with admiration Lim et al.'s paper entitled "An anemic patient with phenotypical β-thalassemic trait has elevated level of structurally normal β-globin mRNA in reticulocytes" in a recent issue of this journal [1].

Although their patient's findings are extremely interesting and puzzling to me, I do not agree with the title of the paper. Because the patient had hepatosplenomegaly (sizes are not given) and marked anemia (Hb: 7 g/dl), his thalassemia should not be called "phenotypical β-thalassemic trait" but rather thalassemia intermedia. Since the α/β ratio was 2.05, by definition, certainly he had thalassemic syndrome. However, some of the findings could be related to Heinz body formation in addition of his thalassemia.

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