

## Case Report

# Leukemic phase of ALK-negative anaplastic large cell lymphoma presenting as leukostasis: the first case report in Thailand

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### Abstract:

*Anaplastic large cell lymphoma (ALCL) is an aggressive T-cell lymphoma characterized by hallmark cells that are CD30-positive. ALCL is subcategorized as anaplastic lymphoma kinase (ALK)-positive and ALK-negative types. The leukemic phase of ALK-negative ALCL is extremely rare and usually has a poor prognosis. We report the first case of the leukemic phase of ALK-negative ALCL in Thailand. A 60-year-old man presented bilateral cervical lymphadenopathy and night sweats for 6 months. He was admitted to the hospital with acute fever, progressive dyspnea on exertion, severe headache and blurred vision. His complete blood count revealed marked leukocytosis ( $352.5 \times 10^9/L$ ) with numerous atypical medium- to large-sized mononuclear cells. The results of his laboratory investigations were compatible with spontaneous tumor lysis syndrome and disseminated intravascular coagulation. The flow cytometry analysis from bone marrow aspiration along with histopathologic findings and immunohistochemistry from bone marrow study were consistent with ALK-negative ALCL. The patient was treated with leukapheresis, renal replacement therapy and high-dose dexamethasone. After achieving hemodynamic stability, a computed tomography scan of the brain was performed due to persistent alteration of consciousness. The results showed extensive intracerebral hemorrhage with severe brain edema and tonsillar herniation. Due to this complication, the treatment plan was adjusted to palliative care with supportive treatment after discussion with his family. The patient subsequently passed away from septic shock.*

**Keywords :** ● ALK-negative anaplastic large cell lymphoma ● Leukemic phase ● T-cell lymphoma

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รายงานผู้ป่วย

มะเร็งต่อมน้ำเหลืองชนิด ALK-negative anaplastic large cell

ที่มาด้วยเม็ดเลือดขาวสูงในเลือด

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บทคัดย่อ

มะเร็งต่อมน้ำเหลืองชนิดเซลล์ใหญ่นาพลาสติก เอแอลเค-เนกาทีฟ (anaplastic large cell lymphoma, ALCL) เป็นมะเร็งต่อมน้ำเหลืองชนิดทีเซลล์ (T-cell) ซึ่งมีลักษณะเซลล์ที่จำเพาะและย้อมติด CD30 โรค ALCL แบ่งออกเป็น 2 ชนิด คือ anaplastic lymphoma kinase (ALK)-positive และ ALK-negative โดยที่ผู้ป่วยโรค ALK-negative ALCL มาด้วยการตรวจพบเซลล์มะเร็งในกระแสเลือดได้น้อย และมักมีพยากรณ์โรคที่ไม่ดี ทางคณะผู้ประพันธ์ได้รายงานผู้ป่วยรายแรกของประเทศไทย เป็นผู้ป่วยชายไทยอายุ 60 ปี คลำพบต่อมน้ำเหลืองที่คอ และเหงื่อออกกลางคืนเป็นเวลา 6 เดือน ได้รับการรักษาในโรงพยาบาลด้วยอาการไข้เฉียบพลัน ร่วมกับเหนื่อยมากขึ้น ปวดศีรษะอย่างรุนแรง และตามัว ผลการสืบค้นทางห้องปฏิบัติการ พบปริมาณเม็ดเลือดขาวสูงมาก ( $352.5 \times 10^9$ /ลิตร) ซึ่งเม็ดเลือดขาวมีขนาดกลางถึงใหญ่ และมีลักษณะของนิวเคลียสที่ผิดปกติ นอกจากนี้ผลการสืบค้นทางห้องปฏิบัติการอื่น ๆ พบว่าเข้าได้กับภาวะ spontaneous tumor lysis syndrome และ disseminated intravascular coagulation ผลการตรวจ flow cytometry ของไขกระดูก และผลย้อมเพิ่มเติมทางพยาธิวิทยา เข้าได้กับการวินิจฉัยโรค ALK-negative ALCL ผู้ป่วยได้รับการรักษาด้วยการทำ leukapheresis การบำบัดทดแทนไต และการให้ dexamethasone ขนาดสูง หลังจากผู้ป่วยมีสัญญาณชีพคงที่ ผู้ป่วยยังคงมีปัญหาเรื่องซีมี จึงได้รับการตรวจภาพรังสีส่วนตัดอวัยวะคอมพิวเตอร์บริเวณสมอง พบเลือดออกในเนื้อสมองหลายจุด ทำให้เกิดภาวะสมองบวมรุนแรง และเกิดการเลื่อนของสมอง (tonsillar herniation) จากภาวะแทรกซ้อนนี้ แพทย์จึงได้ตัดสินใจเรื่องการรักษาร่วมกับครอบครัวของผู้ป่วย ได้ข้อสรุปว่าจะให้การรักษาเป็นแบบประคับประคอง หลังจากนั้น ผู้ป่วยเกิดภาวะช็อกจากการติดเชื้อ และเสียชีวิตในเวลาต่อมา

คำสำคัญ : ● มะเร็งต่อมน้ำเหลืองชนิดเซลล์ใหญ่นาพลาสติก เอแอลเค-เนกาทีฟ ● มะเร็งต่อมน้ำเหลืองในกระแสเลือด ● มะเร็งต่อมน้ำเหลืองชนิดทีเซลล์

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### Introduction

Anaplastic large cell lymphoma (ALCL) is a subtype of CD30+ large T-cell lymphoma, comprising 2% of all adult non-Hodgkin lymphomas<sup>1</sup>. ALCL is defined as the proliferation of large, atypical pleomorphic lymphoid cells, also known as hallmark cells, containing horseshoe-shaped nuclei<sup>2,3</sup>. ALCL is subcategorized as anaplastic lymphoma kinase (ALK)-positive and ALK-negative types<sup>3,4</sup>. ALK-negative ALCL is common among adults, more aggressive than ALK-positive ALCL and usually involves lymph nodes or extranodal sites<sup>2</sup>. The leukemic phase of ALK-negative ALCL is extremely rare and usually has a poor prognosis<sup>5,6</sup>. Our case study describes a patient with an aggressive leukemic phase of ALK-negative ALCL presenting as leukostasis.

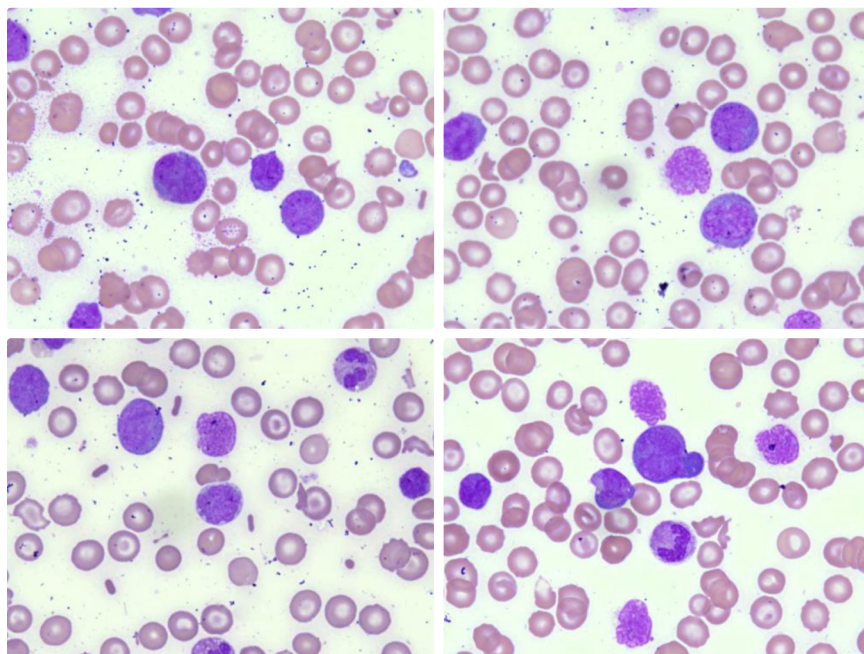
### Case report

A 60-year-old Thai man without significant medical comorbidities presented palpable bilateral neck masses and night sweats for six months. He denied having fever, weight loss or any other constitutional symptoms, and the neck masses slowly enlarged over time. A month prior, fine needle aspiration of the left cervical lymph node was performed, but the result was negative for granuloma or malignancy. He attended a local hospital

presenting a low grade fever and dyspnea on exertion for three days. Subsequently, his symptoms progressed to severe headache, vomiting, blurred vision and respiratory failure. He was intubated, sedated and referred to our hospital for further investigation and treatment.

Physical examination under sedation revealed a body temperature of 37.7°C, heart rate 116 beats per minute, blood pressure 143/79 mmHg, respiratory rate 26 per minute, oxygen saturation 95% with FiO<sub>2</sub> 0.8, mild pallor, moderate jaundice, palpable bilateral multiple lymphadenopathies at cervical, axillary and inguinal areas measuring up to 3x3 cm and hepatosplenomegaly. Neurological examination demonstrated E1VTM4, pupils 3 mm reactive to light in both eyes, normal muscle tone, movement of all extremities with painful stimuli, normal oculo-cephalic reflex and positive gag reflex.

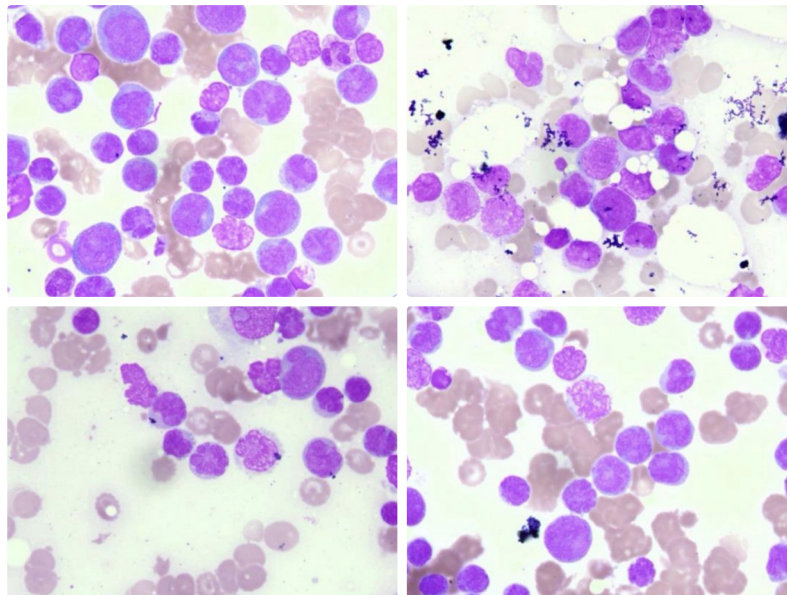
Initial complete blood count showed: hemoglobin 8.6 g/dL, hematocrit 26.2%, mean corpuscular volume 77.7 fL, white blood cell count (WBC) 352.5 x10<sup>9</sup>/L, neutrophils 13%, lymphocytes 67%, monocytes 1%, blasts 19% and platelet count 358 x10<sup>9</sup>/L. The peripheral blood smear demonstrated numerous schistocytes and marked leukocytosis with numerous atypical medium to large mononuclear cells (Figure 1). His blood chemistry results were compatible with tumor lysis syndrome: BUN



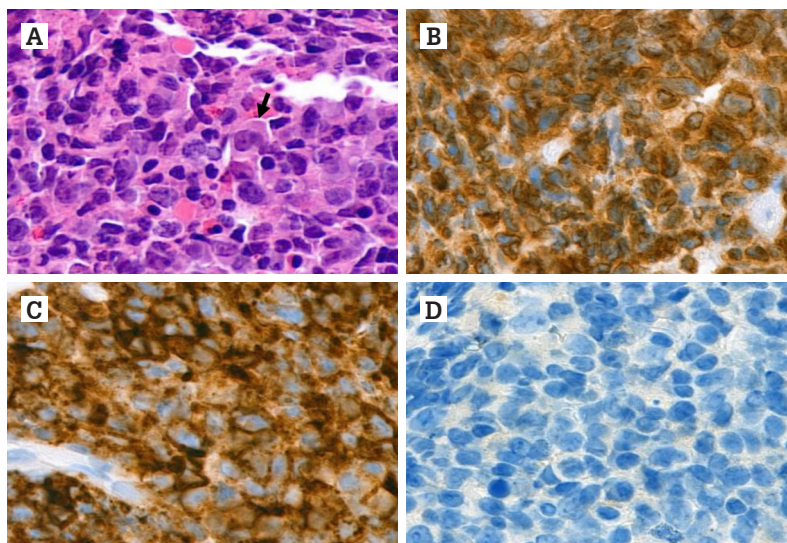
**Figure 1** Patient's blood smear, showing numerous atypical medium to large mononuclear cells

45.9 mg/dL, creatinine 1.86 mg/dL, uric acid 9.6 mg/dL, phosphorus 6.5 mg/dL, potassium 4.8 mmol/L, calcium 8.4 mg/dL and bicarbonate 11 mmol/L. Liver function test showed: SGOT 1,231 U/L, SGPT 422 U/L, ALP 780 U/L, total bilirubin 8.07 mg/dL and direct bilirubin 7.19 mg/dL. Serum lactate dehydrogenase was over 2,500 U/L and serum lactate was high at 9.6 mmol/L. Regarding the coagulation profile, both prothrombin time and activated partial thromboplastin time were prolonged at 22.5 (10.3-12.2) and 40 (23.0-30.8) seconds, respectively. Fibrinogen level was low at 158 mg/dL and d-dimer level was elevated at 16.16 mg/L FEU.

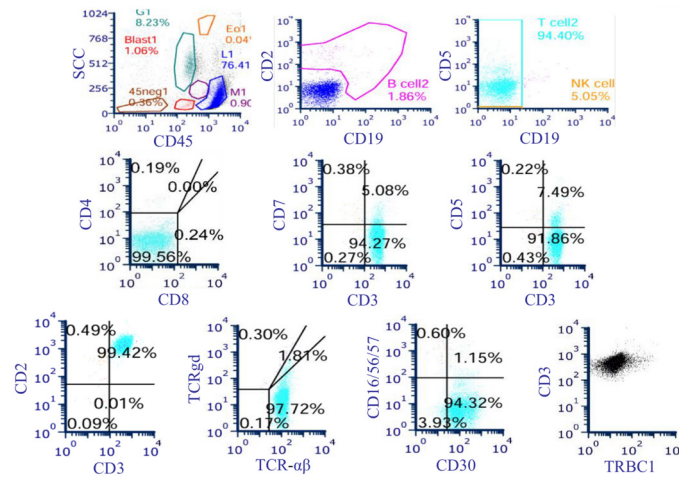
Bone marrow aspiration showed clotted marrow with an increased number of abnormal medium to large mononuclear cells similar to those observed in the peripheral blood smear (Figure 2). Bone marrow biopsy demonstrated hallmark cells with horseshoe-shaped nuclei and diffuse infiltration by abnormal large mononuclear cells expressing CD30, CD2, CD3, Beta-F1 with some also expressing TIA-1. No expression was observed of ALK, CD5, CD7, CD4, CD8, Delta-TCR, CD20, CD25, CD56, EMA, and in situ hybridization for Epstein-Barr virus encoded small nuclear RNA (EBER) was also negative (Figure 3). Flow cytometric analysis of bone marrow



**Figure 2** Bone marrow aspirate smear, showing numerous atypical medium to large mononuclear cells



**Figure 3** (A) H&E stain (400x) showing hallmark cells with horseshoe-shaped nuclei (arrow). (B, C) Immunohistochemistry for CD3 and CD30 (400x) showing strong and diffuse positivity (D) Immunohistochemistry for ALK (400x) was negative



**Figure 4** Flow cytometric analysis with lymphoma panel revealing abnormal lymphoid population expressing CD2, CD3, TCR-  $\alpha\beta$  and CD30, but not expressing CD16/56/57, CD5, CD7, TCR-  $\gamma\delta$ , TRBC1, CD4 and CD8.

aspiration with nonHodgkin lymphoma panel revealed 76.41% lymphocytes on CD45/SSc plot. Most of the lymphocyte population expressed CD2, CD3, TCR- $\alpha\beta$  and CD30, but did not express CD16/56/57, CD5, CD7, TCR- $\gamma\delta$ , TRBC1, CD4 and CD8 (Figure 4). The chromosome analysis from bone marrow aspiration showed complex karyotype and next-generation sequencing for DNA targeted gene sequencing for lymphoid neoplasm revealed *TP53* mutation with variant allele frequency of 86.0%. The findings from flow cytometric analysis of bone marrow aspiration corresponded to the morphology and immunohistochemistry from bone marrow biopsy; therefore, the diagnosis was most likely ALK-negative ALCL with spontaneous tumor lysis syndrome, disseminated intravascular coagulation and leukostasis.

The initial management included hemodynamic support and leukapheresis to rapidly decrease the total WBC count, related to his symptoms of leukostasis, as well as renal replacement therapy to correct multiple electrolyte imbalances and severe lactic acidosis. He received high dose dexamethasone while awaiting a definite diagnosis from the tissue biopsy. After three days of treatment, his hemodynamic and laboratory parameters were improved. However, after reducing the sedative agents, he still did not respond to painful stimuli and had unequal pupil size. A computed tomography scan of the brain showed diffuse, innumerable acute intraparenchymal hemorrhage scattering throughout the

bilateral cerebral hemispheres and cerebellum, acute subarachnoid hemorrhage and extensive diffuse brain edema with 0.4 cm of rightward shift of midline structures and tonsillar herniation (Figure 5).

Because he had extensive intracerebral hemorrhage and severe brain edema with tonsillar herniation, the goal of treatment was palliative with supportive care after discussion with his family. He developed septic shock from *Streptococcus* spp. septicemia and passed away ten days after admission.



**Figure 5** CT brain showing innumerable acute intraparenchymal hemorrhage

### Discussion

ALCL is a mature T-cell lymphoma with uniform, strong expression of CD30 and is usually associated with the aberrant loss of one or more T-cell antigens<sup>3,5</sup>. ALCL is categorized based on the presence or absence of *ALK* translocation<sup>3,4</sup>. ALK-negative ALCL cases are more heterogeneous based on their clinical and epidemiologic features. Compared with ALK-positive ALCL, patients with ALK-negative ALCL have an older median age and more aggressive clinical course<sup>6</sup>. Most individuals affected by ALK-negative ALCL are adults between 40 and 65 years of age, typically presenting with multiple lymphadenopathies and organomegaly. Men are slightly more commonly affected than women, with a male-to-female ratio of 1.5:1. Extranodal sites of involvement include the skin, soft tissue, liver and lungs, while rare sites include the oropharynx, gastrointestinal tract, orbit, brain and testes. The leukemic phase of ALK-negative ALCL constitutes a rare presentation and is associated with a dismal outcome<sup>7</sup>.

Morphologically, the neoplastic cells are large and pleomorphic, with characteristic hallmarks including large lobulated cells with irregular nuclear contours, lacy to clumped chromatin and containing moderate to abundant basophilic cytoplasm (also called horseshoe-shaped nucleus)<sup>2,3</sup>. The neoplastic cells uniformly express CD30

and predominantly express CD4, TIA-1, granzyme B and perforin. The T-cell antigens CD2, CD3, CD5, CD7 and CD8 are variably expressed and cases lacking all T-cell antigens are referred to as having a “null” phenotype<sup>2,3</sup>. Molecular studies have noted *DUSP22* rearrangement has been observed in 30% of ALK-negative ALCL, which is associated with a better outcome than rearrangement of the *TP53* and *TP63*<sup>7</sup>.

The leukemic phase of ALK-negative ALCL is extremely rare and can present either as a primary manifestation or a secondary transformation<sup>8</sup>. Only a few cases of leukemia phase ALK-negative ALCL have been reported in the literature to date, mostly as single case reports<sup>6,8-11</sup>. One report described nine patients with the leukemic phase of ALK-negative ALCL (Table 1)<sup>5</sup>. Immunophenotypically, the leukemic group showed a significantly higher frequency of CD7 than the nonleukemic group [71% (5/7) vs. 19% (5/26);  $p = 0.02$ ]. The karyotype results were available for five leukemic cases, four of which (80%) possessed a complex karyotype. In the analysis for *TP53*, six patients (100%) of leukemic cases showed *TP53* deletion. The report demonstrated that the leukemic presentation of this disease was associated with a greater incidence of absolute lymphocytosis, thrombocytopenia, bone marrow involvement, CD7 positivity, complex karyotype, *TP53*

**Table 1** Clinical features and outcome of 9 patients and our case with leukemic phase of ALK-negative ALCL<sup>5</sup>

Case ID	Age	Sex	WBC ( $\times 10^9/L$ )	Hb(g/dL)	Platelet ( $\times 10^9/L$ )	LN	BM	Outcome
1	61	F	n/a	n/a	n/a	N	n/a	Alive
2	55	M	3.4	10.7	155	P	P	Dead
3	67	M	6.4	13.4	312	N	N	Dead
4	74	M	106.5	11.5	34	P	P	Dead
5	62	M	n/a	n/a	n/a	P	N	Dead
6	58	F	n/a	n/a	n/a	P	N	Dead
7	21	M	n/a	n/a	n/a	N	N	Dead
8	39	M	9.31	10.4	73	N	P	Dead
9	70	M	15.6	15.4	85	P	P	Dead
Our case	60	M	352.5	8.6	358	P	P	Dead

BM, bone marrow; Hb, hemoglobin; LN, lymph node; N, negative; n/a, not available; P, positive; WBC, white blood cell count

deletion and a dismal outcome<sup>5</sup>. Our patient also had complex karyotype with *TP53* deletion but lacked CD7 expression.

Historically, patients with ALK-negative ALCL received anthracycline-based combination chemotherapy such as cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP) or CHOP plus etoposide<sup>12</sup>. In the case series, seven of nine patients (78%) in the leukemic group were treated with CHOP-based chemotherapy. Three of nine patients (33%) achieved complete remission. After a median follow-up of 18 months, 8 of 9 patients (90%) had died. The mortality rate among the leukemic patients was significantly higher than that of the nonleukemic patients<sup>5</sup>. Wong and colleagues reported on an 83-year-old woman with the leukemic phase of ALK-negative ALCL treated with dexamethasone but later died three days after hospitalization<sup>13</sup>. In addition, another case series reported that four patients were treated with the CHOP regimen; however, two patients died within six months, one patient did not achieve complete remission, and one patient was lost to follow-up<sup>5</sup> (Table 2). Based on the ECHELON-2 trial, brentuximab vedotin (BV) combined with cyclophosphamide, doxorubicin and prednisone is considered the standard first-line therapy for CD30-positive peripheral T-cell lymphoma<sup>14</sup>. One report demonstrated the

efficacy of BV in a refractory case of leukemic phase ALK-negative ALCL<sup>10</sup>.

Due to the extreme rarity of the leukemic phase of ALK-negative ALCL, only a limited amount of literature is available concerning treatment and outcomes. More case reports or series of leukemic phase of ALK-negative ALCL cases are required to establish prognostic tools and therapeutic strategies in the future.

### Conclusion

The leukemic phase of ALK-negative ALCL is an extremely rare disease with a dismal outcome. The clinical and pathological presentations can be similar to those of other T-cell lymphomas, leading to difficulties in diagnosis. Advancements in morphology, immunohistochemistry, cytogenetics and molecular studies are needed to enable early diagnosis, leading to prompt treatment. This may reduce the mortality rate among these patients. The optimal intensity of standard chemo-immunotherapy remains unknown due to the limited number of cases. Large registry-based studies are needed to address this unmet need.

### Conflict of interest

The authors declare they have no conflict of interest relevant to the article.

**Table 2** Clinical features, expression of CD7, karyotype and therapies of 5 patients and our case with leukemic phase of ALK-negative ALCL<sup>6,13</sup>

Case ID	Age	Sex	WBC (x10 <sup>9</sup> /L)	Hb(g/dL)	Platelet (x10 <sup>9</sup> /L)	Site of involvement	CD7 positive	Karyotype	Therapies
1	83	F	14.8	11.3	30	LN, spleen, liver	n/a	Complex	Dexamethasone
2	46	M	7.6	10.4	183	LN, BM, CSF	n/a	Complex	CHOP
3	38	M	110	7.6	29	LN, BM	CD7 -	46, XY	CHOP
4	61	F	22.3	8.9	163	LN, BM, spleen, liver	CD7 -	n/a	CHOP
5	46	M	7.1	12	27	LN, BM, spleen	CD7 -	46, XY	CHOP
Our case	60	M	352.5	8.6	358	LN, BM	CD7 -	Complex	Dexamethasone

BM, bone marrow; Hb, hemoglobin; LN lymph node; n/a, not available; WBC, white blood cell count

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