Case Reports

Zbigniew Rudzki[1], Małgorzata Rucińska[2], Wojciech Jurczak[2], Aleksander B. Skotnicki[2], Magdalena Maramorosz-Kurianowicz[3], Andrzej Mruk[3], Krystyna Piróg[4], Grażyna Utych[5], Piotr Bodzioch[6], Maria Srebro-Stańczyk[5], Iwona Włodarska[7], Jerzy Stachura[1]

ALK-Positive Diffuse Large B-Cell Lymphoma: Two More Cases and a Brief Literature Review*

[1]Department of Pathomorphology, Collegium Medicum, Jagiellonian University, Kraków,
[2]Department of Hematology, Collegium Medicum, Jagiellonian University, Kraków,
[3]Department of Chemotherapy, Fryderyk Chopin Memorial Referral District Hospital, Rzeszów,
[4]Department of Pathomorphology, St. Luke District Hospital, Tarnów,
[5]Department of Chemotherapy, St. Luke District Hospital, Tarnów,
[6]Department of General Surgery & Oncology, St. Luke District Hospital, Tarnów,
[7]Department of Human Genetics, Catholic University Leuven, Leuven, Belgium

Anaplastic lymphoma kinase (ALK)-positive diffuse large B-cell lymphoma (DLBCL) is a rare, recently defined tumor distinct in many aspects from ALK-positive anaplastic large cell lymphoma (ALCL). We present two additional cases of ALK+DLBCL recently diagnosed in our department and a review of literature. A 48-year old man presented with a large upper neck mass growing slowly over 18 months. Histologically the tumor was diagnosed as an ALK-positive diffuse large B-cell lymphoma with plasmablastic features. Large, frequently intrasinusoidal tumor cells expressed CD138, EMA, weakly IgA and kappa, but were negative for other B-cell markers, T-cell markers and CD30. The ALK staining was cytoplasmic with the increased intensity in the Golgi area. At the diagnosis the patient manifested with the stage IIIB. Three courses of CHOP resulted in partial and only transient remission. The patient died of massive bleeding from his decomposing tumor 3 months after the diagnosis. A 49-year old man complaining of abdominal pain revealed abdominal lymphadenomegaly and a gastric infiltrate, involving the deep portions of the gastric wall. The tumor showed immunoblastic/anaplastic morphology, with some Reed-Sternberg-like cells positive for ALK. ALK immunostaining was cytoplasmic, weak in a routine immunostain, enhanced with double (proteinase + pressure cooker) antigen retrieval. FISH was consistent with the t(2;5)/nucleophosmin(NPM)-ALK rearrangement. The tumor demonstrated similar "null" B/T phenotype with positivity for IgA, lambda, EMA and LCA. The patient (stage IVB) currently undergoes chemotherapy. ALK-positive DLBCL affects mostly middle-aged men, shows generally poor but stage-dependent prognosis (at least 60% mortality rate), presents typically as a lymph node-based disseminated disease, and very rarely involves the bone marrow. Genetic studies showed that the majority of ALK+DLBCL cases are characterized by the clathrin (CLTC)-ALK fusion and in a few cases the NPM-ALK rearrangement has been found.

Introduction

Anaplastic lymphoma kinase (ALK) gene was identified in 1994 as a gene targeted by a t(2;5)(p23;q35) translocation, characteristic for a subset of CD30-positive large T- or null cell lymphomas with anaplastic morphology [13]. The translocation fused ALK to the nucleophosmin (NMP) gene, resulting in ALK overexpression detectable at the protein level by immunohistochemistry. The ALK-positive ALCL, recognized as an entity in the REAL and WHO classifications, and colloquially called "ALKomas", are relatively frequent, particularly in pediatric population. Although these tumors are

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naturally highly aggressive, they showed a favorable prognosis upon the appropriate therapy [10]. So far, at least 9 variant translocations involving the ALK gene and different partner genes were identified in these lymphomas (reviewed in [16]).

The expression of ALK protein in human is otherwise a rare phenomenon. In normal tissues it is restricted to certain central nervous system cells, whereas in neoplasia other than ALKoma it has been found in a part of inflammatory myofibroblastic tumors, rhabdomyosarcomas and neuroblastomas [11]. In 1997, Delsol et al. reported seven cases of B-cell lymphomas expressing ALK but lacking t(2;5) [8]. For the time being this extremely rare tumors had been recognized as "Diffuse large B-cell lymphoma with expression of full-length ALK" by WHO classification of lymphoma [10]. In 2003, a few independent groups published altogether 11 subsequent cases and identified t(2;17)(p23;q23) as the most frequent translocation in this lymphoma subtype [6, 9, 15]. The t(2;17) juxtaposing the ALK and clathrin (CLTC) genes, had been previously found in some ALKomas [5, 14, 17]. So far only 23 cases of ALK-positive DLBCL were published in the MEDLINE-indexed literature. In this report we present two additional cases and briefly review the published cases.

CASE DESCRIPTIONS

Case 1

A 48-year old man was referred to the Department of Hematology, Collegium Medicum, Jagiellonian University, Kraków, after recovery from a car accident resulting in a multi-organ injury. Before the accident he reported an 18-month history of slowly growing upper neck tumor at his right side. At admission the tumor measured 10×15 cm with a 12 cm bleeding ulceration. The tumor growth was accompanied by progressive fatigue, significant (25 kg) weight loss and fever, but the patient did not seek medical assistance until the injury. The physical examination demonstrated also ipsilateral supraclavicular (10×5 cm), infraclavicular (5 cm) and axillary (8×5 cm) lymphadenopathy with the right upper limb edema. The liver was enlarged, measuring 19 cm in the midline. Immediately after the accident, the patient was splenectomized due to a bleeding resulting from the spleen rupture after the car crash. The abdominal and thoracic computed tomography, abdominal ultrasound, and chest X-ray did not show any other abnormalities. He reported a significant familial history with his two sisters and their mother diagnosed with the breast cancer.

Laboratory tests demonstrated elevated serum lactate dehydrogenase (1056 U/L, norm to 480 U/L), profound anemia (erythrocytes $2.12x10^6/\mu L$, hemoglobin 4.9 g/dL, packed red cell volume 16.1%), marked thrombocythemia (platelets $1893x10^3/\mu L$) and granulocytic leukocytosis (white blood cells $31.9\times10^3/\mu L$, with 78% segmented neutrophils, 4% bands, 2% promyelocytes, 4% eosinophils, 8% lymphocytes, 4% monocytes, no atypical cells).

The patient was referred from a provincial hospital with a sample of the upper neck tumor consisting of two hematoxylin and eosin slides and two corresponding paraffin blocks. This sample was taken during the post-injury surgical procedure, and was initially diagnosed in the referring institution as "carcinoma", and subsequently as "lymphoma, not otherwise specified" by another general pathologist. The spleen specimen was unavailable, but according to the patient's chart, the spleen was unremarkable save the features of rupture proportional to the strength of the mechanical injury.

Upon the final diagnosis in the University facilities, the patient was referred for the specific lymphoma treatment to the tertiary regional oncological center. The bone marrow aspiration and trephine biopsies performed prior to the therapy showed only marked but nonspecific reactive pathology and were negative for lymphoma. The patient was treated with 3 courses of CHOP with only transient reduction of the tumor mass (50%) followed by a quick relapse and progression. Of note, his platelets gradually increased reaching $3{,}200\times10^3/\mu L$, although white blood cells dropped to normal limits. Three months after the diagnosis the patient died of massive bleeding from the ulcerated residual tumor. The autopsy was not done.

Case 2

A 49-year old male presented with a one-month history of abdominal pain, significant (10 kg) weight loss, night sweats and fever. There was no peripheral lymphadenopathy on admission. Computed tomography revealed distal gastric tumor measuring 50×70 mm, enlargement of the majority of abdominal lymph nodes, enlarged homogenous liver (190 mm) and a normal spleen. Conglomerates of enlarged lymph nodes were also seen in the thorax, measuring 56×18 mm (periaortic) and 23×21 mm (esophageal). The mediastinum was uninvolved.

The patient was anemic with hemoglobin 10.0 g/L, erythrocytes $3.41\times10^6/\mu L$, and packed red cell volume 28.6%. Platelets were slightly elevated to $559\times10^3/\mu L$. The number of white blood cells was normal ($6.6\times10^3/\mu L$), with marginal monocytosis (14.9%), 21.3% lymphocytes, 59.3% segmented neutrophils, 4.2% eosinophils and 0.6% basophil granulocytes. Serum lactate dehydrogenase was 706 IU/L. Serum and urine protein electrophoresis revealed a monoclonal protein peak, identified as IgG lambda on

immunofixation. Serum gamma globulins were slightly raised (21.9 g/L).

Explorative laparotomy with partial gastrectomy resulted in a histological diagnosis of lymphoma (see below). Shortly after the recovery from the surgery, the patient developed bilateral axillary (up to 20 mm) and left lower neck (45 mm conglomerate) lymphadenomegaly. Bone marrow examination was not performed. The chemotherapy was initiated with the CHOP regimen and continued with three series of CHOP-14. Only a transient response was achieved and the disease progressed at the final stage of chemotherapy. Currently the ESHAP regimen is taken into consideration.

Material and Methods

Upon the inspection of the original slides the submitted paraffin blocks were cut into 3 μm sections stained with hematoxylin and eosin, Giemsa and PAS methods. Subsequent slides were immunostained with antibodies specific for epithelial, leukocytic, proliferation/activation markers and ALK (see Table 1), using the DAKO autostainer.

FISH was performed on interphase nuclei isolated from five 20 μm sections of the formalin-fixed paraffin-embedded tumor material using Paraffin Pretreatment Kit (Vysis, Downers Grove, Illinois, USA). The status of the ALK gene (2p23) was investigated with LSI ALK Dual Color, Break Apart Rearrangement Probe (Vysis, Downers Grove, Illinois, USA). This assay comprises a set of probes flanking the 3'- and the 5'-end regions of ALK labeled with SpectrumOrange- and SpectrumGreen-dUTP, respectively. The clathrin (CLTC) gene at 17q23 and the NPM gene at 5q35 were investigated with a newly developed dual color FISH assays consisting of two pairs of Bacterial Artificial Chromosome (BAC) clones flanking the each of genes (http://www.ensemble.org). The CLTC clones, RP11-118K23 and RP11-301K02 were labeled with SpectromGreen-dUTP, and RP11-622H01 plus RP11-50F16, were labeled with SpectrumOrange-dUTP using nick translation method. The NPM clones, RP11-45L16 and RP11-768O14, were labeled with SpectromGreen-dUTP, and RP11-20O22 was labeled with SpectrumOrange-dUTP (Vysis, Downers Grove, Illinois, USA). BAC clones were ob-

TABLE 1
Immunostaining of the ALK-positive diffuse large B-cell lymphoma

Antibody specificity	Supplier	Titer	Antigen retrieval	Case 1	Case 2
ALK	DAKO	1:25	microwave, citrate buffer pH=6.0*	(+)	(+/-)
Ki67 (MIB1)	DAKO	1:50	microwave, citrate buffer pH=6.0	(+) 50% - 70%	(+) 20%-30%
CD45 (LCA)	DAKO	1:100	microwave, citrate buffer pH=6.0	(+/-)	(+)
CD138	DAKO	1:100	microwave, citrate buffer pH=6.0	(+)	(-/+)
IgA	DAKO	1:300	proteinase K	(-/+)	(+/-)
IgG	DAKO	1:500	proteinase K	(-)	(-)**
IgM	DAKO	1:300	proteinase K	(-)	(-)
kappa	DAKO	1:1600	-	(-/+)	(-)
lambda	DAKO	1:2000	-	(-)	(+)
EMA	DAKO	1:50	-	(+)	(+)
CD20	DAKO	1:50	microwave, citrate buffer pH=6.0	(-)	(-)
CD79a	DAKO	1:50	microwave, citrate buffer pH=6.0	(-)	(-/+)
CD3	Novocastra	1:100	microwave, citrate buffer pH=6.0	(-)	ND
CD5	Novocastra	1:50	microwave, EDTA buffer, pH=8.0	ND	(-)
CD45RO	DAKO	1:50	microwave, citrate buffer pH=6.0	(-)	(-)
CD30	Novocastra	1:40	microwave, citrate buffer pH=6.0	(-)	(-)
cytokeratin 20	DAKO	1:50	microwave, citrate buffer pH=6.0	(-)	ND
cytokeratin 7	DAKO	1:50	microwave, citrate buffer pH=6.0	(-)	ND
cytokeratin, poly.	DAKO	1:50	microwave, citrate buffer pH=6.0	(-)	(-)
LMP (EBV)	Novocastra	1:50	proteinase K	(-)	ND

(+): all cells clearly positive; (+/-): some cells strongly positive, most negative; (-/+): some cells weakly positive; most negative; (-): all cells negative; *for case 2 marked enhancement of staining was achieved using combined unmasking protocol (proteinase K digestion followed by high-pressure cooking in EDTA buffer, pH=8.0); **despite serum monoclonal IgG peak.

tained from the Roswell Park Cancer Institute RPCI11 libraries (http://www.chori.org/BACPAC).

Results

Case 1

The consultation material consisted of three cross-sections of up to 8 mm-diameter, identifiable as lymph node fragments, composed largely of necrotic tissue, areas of fibrosis and nonspecific granulation. Additionally there were areas of diffuse infiltrate of very large atypical cells demonstrating ample eosinophilic cytoplasm, occasionally with a paranuclear clearing corresponding to the Golgi zone. The nuclei were regular, usually with a prominent central eosinophilic nucleolus. There were no "hallmark cells" of ALKoma with kidney-shaped nuclei, and many atypical cells showed cytological features reminiscent of highly atypical and large plasma cells. Not infrequently the atypical cells occupied distended lymph node sinuses (Figs. 1 and 2). The proliferative activity was high, approaching 100 mitoses/10 high-power fields, and so was the expression of Ki67 found in 50%-70% of the large cells. The results of immunostaining are summarized in the Table 1. Notably, the ALK immunoreactivity was granular and cytoplasmic, with the strongest staining within the Golgi zones (Fig. 3). The ALK staining pattern suggested the presence of CLTC-ALK, however, FISH applied to demonstrate this rearrangement was unsuccessful.

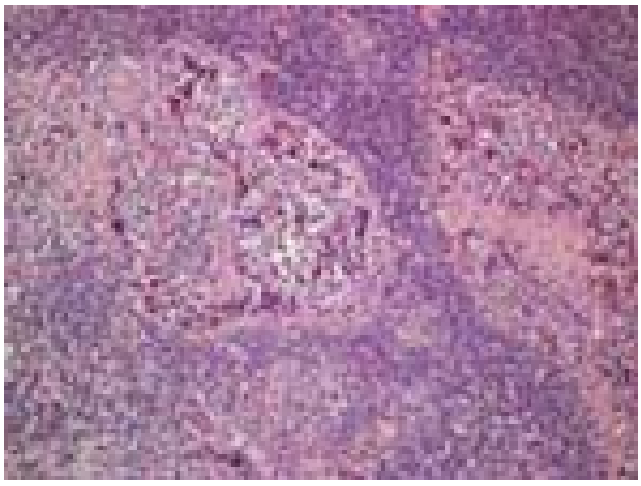

Fig. 1. Case 1: predominantly intrasinusoidal infiltrate of ALK-positive diffuse large B-cell lymphoma. HE. Obj. 20×.

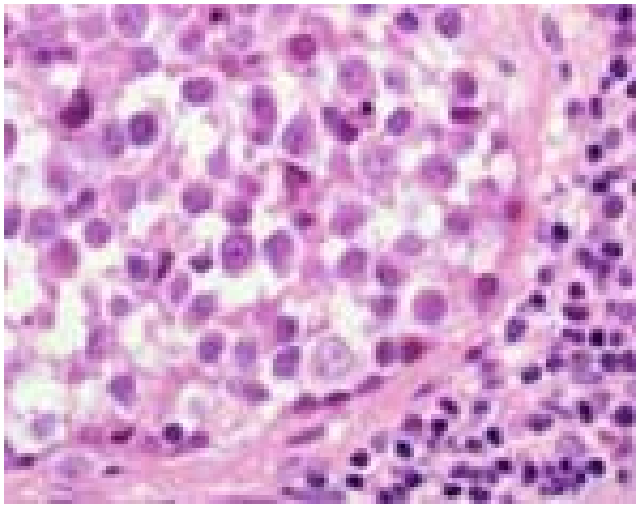

Fig. 2. Case 1: plasmablastic morphology of the neoplastic cells. HE. Detail from obj. 60×.

Case 2

The histological material (5 paraffin blocks) encompassed a diffuse or polycyclic, partially necrotic infiltrate,

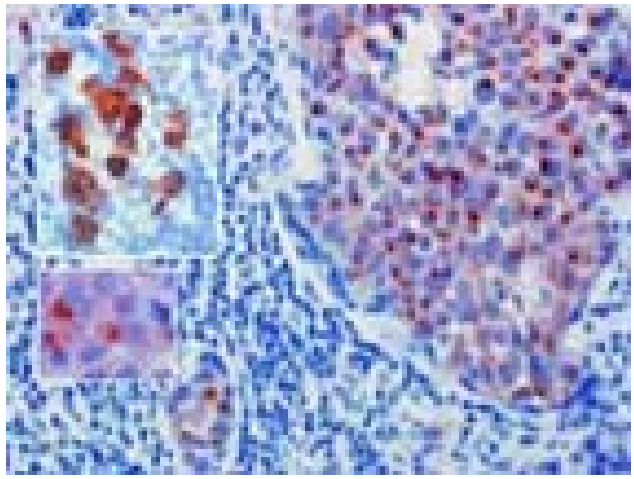

Fig. 3. Case 1: ALK expression in the ALK-positive DLBCL limited to the cytoplasm, with particularly strong reaction within the Golgi zone. APAAP technique. Obj. 60×. The insets compare the ALK staining in the CD30-positive anaplastic large T-cell lymphoma (nuclear and cytoplasmic, upper inset), and in the ALK-positive DLBCL (cytoplasmic only, with perinuclear increase of intensity, lower inset).

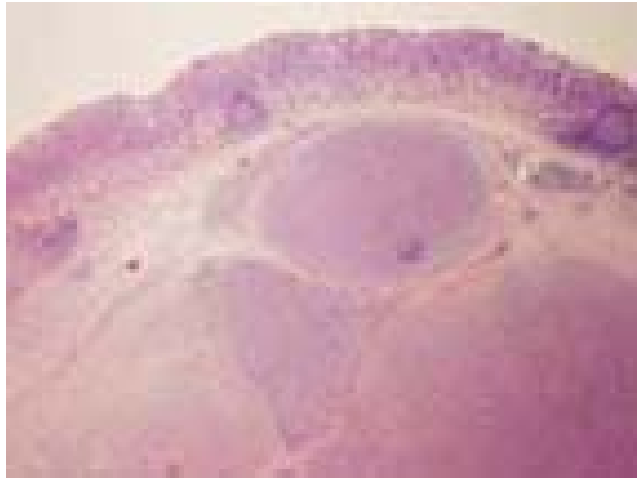

Fig. 4. Case 2: low-power view of the gastric wall infiltrated by ALK-positive large B-cell lymphoma. The muscularis mucosae and the mucosa are uninvolved, and most probably the tumor spreads to the stomach from deep lymph nodes. HE. Obj. 2×.

occupying most of the gastric wall, with an uninvolved mucosa (Fig. 4). The infiltrate was dominated by the large atypical immunoblastic cells with scattered monstrous cells morphologically resembling the Hodgkin or Reed-Sternberg cells (Fig. 5), but with a conspicuously different immunophenotype pointing out at the plasmacytic differentiation (Table 1). The mitotic activity was high (approximately 80 mitoses per 10 high-power fields). The neoplastic cells did not fill larger veins or arteries but many distended capillary-type vessels were packed with atypical immunoblasts. This was particularly conspicuous in the CD34 immunostaining (Fig. 6). Using the routine immunostaining protocol the expression of ALK was documented only in some particularly large cells, however, upon the drastic unmasking procedure of the type we use for cyclin D1 (proteinase digestion followed by high-pressure cooking) most of the neoplastic cells revealed cytoplasmic staining (Fig. 7). The genomic rearrangement underlying ALK expression in this case was initially studied by FISH with double color break apart from assays for the ALK and CLTC genes. These studies showed rearrangement of ALK (split of signals) (Fig. 8A) in a significant portion of analyzed interphase cells and a normal FISH pattern of CLTC probes [2]. These results indicated involvement of the ALK gene but excluded t(2;17)(p23;q23). As t(2;5)(p23;q35) has been also reported in a minority of ALK+DLBCL, we further analyzed the status of NPM by FISH and indeed, detected a rearrangement of this gene (Fig. 8B). Altogether, ALK expression in this case was associated with the typical NPM-ALK rearrangement due to t(2;5)(p23;q35).

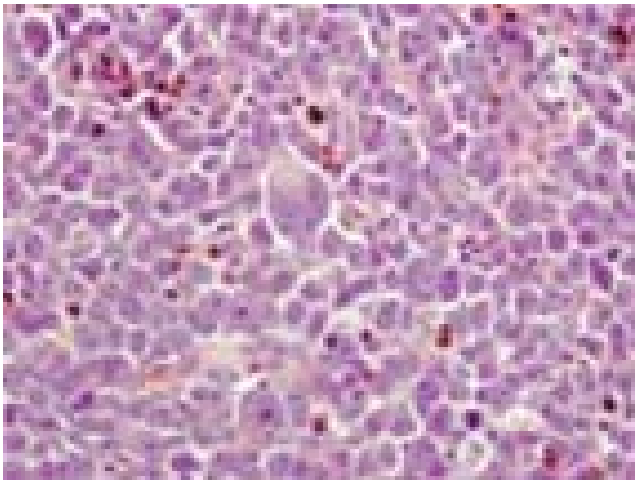

Fig. 5. Case 2: highly atypical neoplastic cells, some resembling the Reed-Sternberg cells. HE. Obj. 60×.

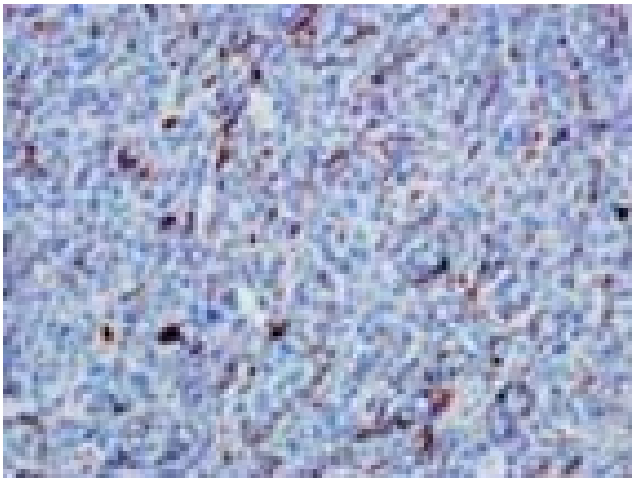

Fig. 6. Case 2: intrasinusoidal location of many neoplastic cells demonstrated upon immunostaining of capillaries with anti-CD34 monoclonal antibody. APAAP technique. Obj. 40×.

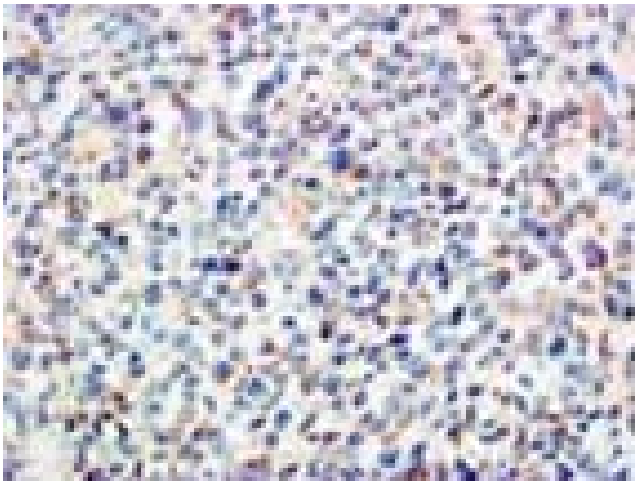

Fig. 7. Case 2: cytoplasmic ALK immunostaining visualized using the intense antigen unmasking compromising tissue quality but visualizing more ALK-positive cells. APAAP technique. Obj. 60×.

Discussion

Diagnosis of ALK-positive DLBCL requires first the identification of the hematopoietic nature of the tumor, and then solving the problems associated with the “null” phenotype. The most obvious initial element of differentiation is a lymph node spread of a carcinoma from an unknown primary. The somehow epithelioid appearance of neoplastic cells together with their preferential intrasinusoidal location strongly suggest a carcinoma, however, the clinical features (particularly no detectable visceral “primary”) and the prominent Golgi area should constitute a warning that this apparently obvious solution may be false. The clue to the diagnosis of ALK-positive DLBCL is its plasmacytoid or immunoblastic cytology together with the expression of at least some markers of late (plasma cell-like) B-cell differentiation, like CD138, VS38 and immunoglobulins in the context of negativity for more commonly used B-cell markers,

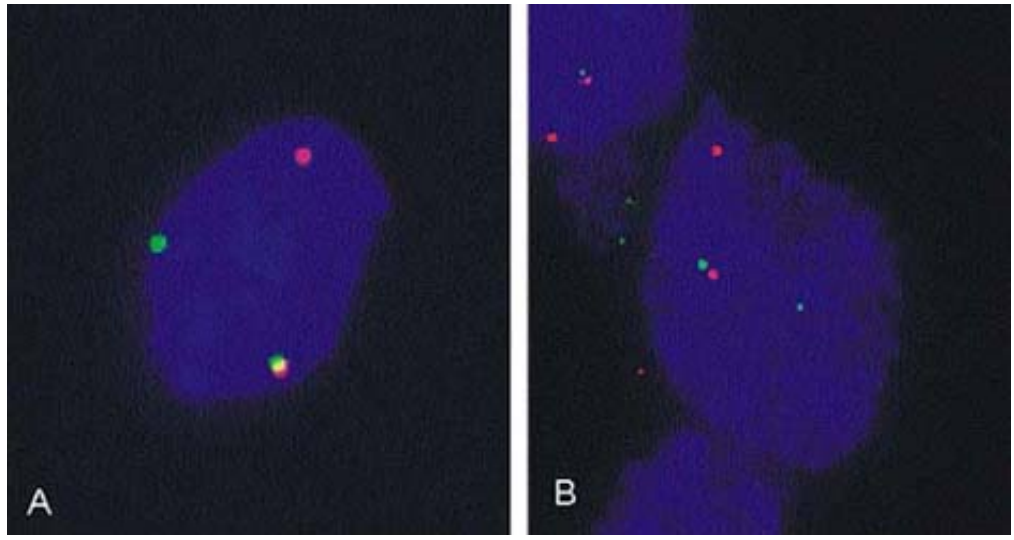

Fig. 8. Examples of FISH analysis performed in case 2 using dual color break apart LSI ALK (A) and NPM (B) assays. Note split of red and green signals in both experiments hallmarking genomic rearrangements of the ALK and NPM genes.

TABLE 2

Comparison of histological and immunohistochemical features of ALK-positive anaplastic large cell lymphoma and ALK-positive diffuse large B-cell lymphoma

	ALKoma	**ALK(+) DLBCL**
cellular morphology	anaplastic (at least some cells) with "hallmark" cells	plasmablastic or immunoblastic
intrasinusoidal dissemination	(+)	(+)
"null" phenotype	(+)	(+)
EMA	(+)	(+)
LCA (CD45)	(-/+)	(+/-)
CD30	(+)	(-)
lineage of origin by molecular studies	T	B
ALK-involving translocation	t(2;5)/NPM-ALK (up to 70%) and at least 9 variant translocations, including t(2;17)/CLTC-ALK (~30%)	t(2;17)/CLTC-ALK (most) and t(2;5)/NPM-ALK (rare)
ALK expression pattern	cytoplasmic and nuclear in cases with NPM-ALK, and cytoplasmic, membrane and granular in cases with variant translocations	granular cytoplasmic in cases with CLTC and cytoplasmic in cases with NPM-ALK

like CD20, and frequently CD79a. All these features should prompt the ALK staining. Despite some similarities between ALKoma and ALK-positive DLBCL, particularly not infrequent EMA expression and the "null" phenotype in a limited panel of pan-leukocytic, B- and T-cell markers, these two lymphomas show several important immunohistochemical and histological differences, summarized in the Table 2.

Of special interest are the peculiarities of the ALK immunostaining. Most cases of ALKoma show cytoplasmic and nuclear expression, correlating with the presence of NPM-ALK fusion resulted from t(2;5)(p23;q35). In contrast, most reported ALK-positive DLBCL cases were associated with the CLTC-ALK rearrangement due to t(2;17)(p23;q23) and showed the ALK expression limited to the cytoplasm, particularly to the Golgi area. Our FISH studies aimed at identification of gene rearrangements underlying ALK expression in the present ALK+DLBCL cases, failed in the case 1 (with cytoplasmic granular staining suggesting CLTC-ALK) and showed the NPM-ALK rearrangement in the case 2, in which the staining pattern was weak and cytoplasmic.

The ALK immunostaining intensity in our case 1 was strong and universal, however, in the case 2 in the original routinely stained slides it was only focal (some particularly large cells) and could have been easily overlooked had we had a smaller material. Universal expression of the ALK protein was confirmed in the case 2 using a drastic double antigen retrieval method. It is thus conceivable, that more diffuse large B-cell lymphomas may in fact represent

TABLE 3
Published cases of ALK-positive anaplastic large B-cell lymphoma

Reference	Number of cases	DOD number of cases (survival)	CR number of cases survival (stage)	PR	Lost to follow-up	Sex/ age	Stage	ALK expression/ fusion
Delsol et al. Blood 1997 [8]	7	4 (9-33m)	2 13y (I), 14m (?)	-	1	M15, M37, M44, M51, M53, M60, F67	III/IV: 5 II: 1 I: 1	cytoplasmic/ not NPM-ALK (presumed to express "full length ALK")
Gascoyne et al. Blood 2003 [9]	6	2 (6m, 26m)	**2** 27m (I) 27m (III)	**1**	1	M46, M48, M49, M51, M58, F45	IV:3 III:1 I:1 ?:1	all granular cytoplasmic/ CLTC-ALK
De Paepe et al. Blood 2003 [6]	3	1 (3m)	2 44m (II) 27m (II)		-	M10, M26, F13	II:2 III:1	all granular cytoplasmic/ CLTC-ALK
Onciu et al. Blood 2003 [15]	2	1 (24m)	1 13y (II)	-	-	M16, M10	III:1 II:1	cytoplasmic and cytoplasmic + nuclear/ both NMP-ALK
Chikatsu et al. Mod Pathol 2003 [3]	1	1 (11m)	-	-	-	F36	IV	granular cytoplasmic/ CLTC-ALK
Adam et al. Am J Surg Pathol 2003 [1]	1	1 (14m)	-	-	-	M35	II	cytoplasmic and nuclear/NPM -ALK
McManus et al. Hum Pathol 2004 [12]	1	-	1 2y (IIe)	**-**	-	M21	IIe (stomach)	granular cytoplasmic/ CLTC-ALK
Colomo et al. Am J Surg Pathol 2004 [4]	1	1 (8m)	-	-	-	M34	III	granular cytoplasmic/ not tested
Bubała et al. Pediatr Blood Cancer 2005 [2]	1	1 (5m)	-	-	-	M9	IV	granular cytoplasmic/ CLTC-ALK
Present report	2	1 (3m)	1: under treatment, resistant		-	M48 M49	III IV	1. granular cytoplasmic/ not tested, 2. weak, cytoplasmic/ NPM-ALK

DOD: died of the disease; CR: complete remission; PR: partial remission (as defined by the original authors).

ALK-positive tumors skipping the detection due to a weak and focal ALK immunoreaction upon routine protocols that are otherwise fully satisfactory for ALK-positive ALCL.

In contrast to ALKomas, all but one published ALK-positive DLBCL were CD30-negative [12]. They tend to express EMA, which is in accordance with their plasmacytic differen-

TABLE 4
Clinical features of ALK-positive anaplastic large T-cell lymphoma compared with ALK-positive diffuse large B-cell lymphoma based on the characteristics of the cited published cases

	ALKoma	ALK(+) DLBCL
Typical primary site/dominant presentation	lymph nodes (90%) and/or extranodal (60%)	mostly lymph nodes ~9% extranodal
Epidemiology	marked male predominance mean age 22-30 years ~3% of NHL in adults 3-10% of NHL in children	marked male predominance most middle-aged (mean 37 years), 20% in children very rare, probably << 1% of DLBCL
Prognosis	good: 80% 5-year survival although ~75% present in stages III/IV	intermediate or poor (over 60% mortality rate) may be strongly stage-dependant

tiation, and are usually IgA-positive. If the proliferation fraction is reported, it is typically very high, differing ALK-positive DLBCL from extramedullary plasmacytomas and plasma cell myelomas with the soft tissue involvement. The differential diagnosis includes also the recently described plasmablastic lymphoma of the oral cavity, which is ALK-negative, and develops typically in the setting of immunosuppression [7]. Two other "null" phenotype lymphomas of the B-cell lineage: the pyothorax-associated lymphoma and the primary effusion lymphoma (body cavity-based lymphoma) are also ALK-negative, and occur in different, characteristic clinical settings [10].

The biology of ALKoma, including its highly predictable clinical course, is currently better known, whereas the data on the clinical features of ALK-positive DLBCL are still limited. The Table 3 summarizes the currently published cases of ALK-positive DLBCL and the Table 4 compares the clinical features of both entities.

The age of the patients diagnosed with the ALK-positive DLBCL ranged from 9 to 67 years (mean 37.2 years, median 44 years). There were 5 children aged 15 years or less (20%), and only 4 females (M:F ≈ 5:1). Nearly half (48%) of the patients were men aged 30–55 years. For most tumors the dominant presentation was lymphadenopathy, frequently generalized, although two cases were primarily extranodal: one gastric [12], and one most probably ovarian [3]. In our case 2, it is unclear whether the tumor was primarily gastric or deep lymph-node based. The latter primary location is more probable, as the stomach involvement was limited to its deeper portions, whereas most primary stomach lymphomas develop in the mucosa.

Despite of a low number of published ALK-positive DLBCL cases, the prognosis of this lymphoma subtype seems to be much worse than that of T/null ALKoma. The overall mortality rate was 60%. In contrast to ALKoma, whose prognosis is usually good even at the advanced stages, there seems to be an adverse correlation between the stage at presentation and prognosis in ALK-positive DLBCL. Sixteen out of 24 cases published (66.7%) with available staging data, presented with the advanced disease (stage III or IV). Distribution of the stage among the survivors was markedly different with six out of eight survivors presenting with stage I or II lymphoma, and only one in stage III (in one case the published data do not include the stage of the survivor). The survivors were treated using different protocols, employing aggressive chemotherapy, occasionally supplemented with irradiation. Despite frequent advanced disease at presentation, in only one case there was an evidence for bone marrow involvement [3], which seems to be a unique and interesting feature of this entity.

The unusual aspect of our case 1 is a very long natural history of the tumor (18 months prior to the diagnosis), contrasting with the histological features of its high proliferative activity. We can only speculate that the high proliferative capacity of the tumor was counter-balanced by necrotic events and/or intense apoptosis. The death of this patient can not be directly solely attributed to the tumor progression, as the patient succumbed to a massive bleeding from his partially decomposing and ulcerated tumor mass. Another unusual feature, extreme thrombocytosis, surpassing 3 million per microliter, has to be interpreted as a reactive phenomenon. The thrombocytosis, although not so striking (559,000 per microliter) was also found in our case 2.

To summarize, from the 25 published cases of ALK-positive DLBCL emerges a picture of a specific disease entity characterized typically by a lymph node-based disease affecting mostly the middle-aged men, frequently showing aggressive behavior, a negative prognostic impact of the advanced stage, and a strikingly rare bone marrow involvement.

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Address for correspondence and reprint requests to:
Zbigniew Rudzki M.D.
Department of Pathomorphology
Collegium Medicum, Jagiellonian University
Grzegórzecka 16, 31-531 Kraków
Phone: (+48) 12 4215210
Fax: (+48) 12 4119725
E-mail: mprudzki@cyf-kr.edu.pl