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Case Study

Interdigitating Cell Sarcoma

—— A report of an autopsy case and literature review ——

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A 58-year-old Japanese man developed discomfort of his left neck, gradually increasing left chest pain, and weight loss (15 kg over six months). His primary physician noted generalized lymphadenopathy, and a neck lymph node was excised for diagnosis. When he was admitted to our hospital, he had severely decreased appetite accompanied by a large intra-abdominal mass. The lymphadenopathy was temporarily reduced by CHOP (cyclophosphamide, hydroxydoxorubicin/adriamycin, vincristine/oncovin, prednisone) chemotherapy, but pancytopenia and hepatomegaly persisted. After 3 courses of therapy, tumor cell regrowth was evident in peripheral blood and bone marrow and his course rapidly declined, with complications from hemophagocytic syndrome. He expired after a total course of 6 months. A postmortem examination was performed 2 hours after death. A final diagnosis of interdigitating cell sarcoma was made based on histological and immunohistochemical analyses of the biopsied lymph nodes and autopsy materials. His clinical course was extremely aggressive, and chemotherapy was not effective. Discussion of this case provides important insight into the clinicopathological features and treatment of this neoplasm.
Key words lymph node, dendritic cell, interdigitating cells (IDC), hemophagocytic syndrome (HPS)

INTRODUCTION

Interdigitating cells (IDCs) are a type of dendritic cell, which reside in T-cell dependent areas of lymphoid tissues and are essential for initiation of a variety of immune responses[1-3]. Because tumors derived from dendritic cells are relatively rare, their general clinicopathological features, including the degree of biological aggressiveness and applicable treatment, have yet to be characterized. Recently, an increased number of cases of this type of tumor have been reported[4-30], in part due to increased recognition by pathologists and improved identification of dendritic cells and their neoplastic counterparts by new antibodies specific to human dendritic cells. In the new WHO histological classification of tumors of hematopoietic and lymphoid tissues (published in 2001)[31], dendritic cell tumors were classified as an independent category termed "histiocytic and dendritic cell neoplasms." We present here a case of a dendritic cell tumor with an aggressive clinical course.

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CASE REPORT

A 58-year-old Japanese man, with a 10 year history of diabetes mellitus, complained of 2 months of discomfort of the submandibular portion of his left neck. He subsequently noted increasing left sided chest pain and malaise. His body weight decreased remarkably (15 kg over 6 months). His primary physician detected generalized lymphadenopathy and referred him to a general hospital for further examination and appropriate treatment. His family history was unremarkable.

On admission to the general hospital, mild anemia was detected (RBC 367 × 10^4/ μl, Hb 12.2 g/dl), but his WBC (6,100/ μl) and platelet (24.7 × 10^4/ μl) counts were within the normal range. His peripheral blood differential included 47.0% neutrophils, 33.8% lymphocytes, 12.6% monocytes, 5.9% eosinophils, and 0.5% basophils. No atypical lymphocytes were identified. The serum soluble interleukin-2 receptor (sIL-2R) concentration was extremely high (2,230 U/ml). Other laboratory data including total protein (8.8 g/dl), albumin (3.7 g/dl), γ -globulin (46.1%), GOT (34 IU/l), GPT (17 IU/l), LDH (390 IU/l), ALP (314 IU/l), BUN (12.2 mg/dl), creatinine (0.8 mg/dl), and C-reactive protein (0.68 mg/dl) were within the normal range.

Lymphadenopathy of up to 3 cm in diameter of the superficial lymph nodes (LNs) in his left neck and inguinal region was objectively apparent. One of left neck LNs was excised for pathological examination. Mild hepatomegaly

was also noticed. On computed tomography, enlarged neck, axillary, and para-aortic lymph nodes and hepatosplenomegaly were recognized. Gallium scintigraphy demonstrated multiple hot lesions in bilateral neck, right axillary, para-aortic, and mesenteric nodes. ^{99}mTc bone scintigraphy did not reveal any abnormal accumulation.

When he arrived at our hospital, his performance status according to the Eastern Cooperative Oncology Group (ECOG) scale[32] was level 4. He complained of severely decreased appetite accompanied by the presence of a large intra-abdominal mass. After the first course of chemotherapy with CHOP (cyclophosphamide, hydroxydoxorubicin/adriamycin, vincristine/oncovin, predonisone), his lymphadenopathy was temporarily reduced and his performance status improved to level 2. However, after the third course of chemotherapy, he rapidly developed pancytopenia, severe hepato-splenomegaly, and tumor cell involvement of the bone marrow and peripheral blood. He declined clinically and died after a total course of 6 months. A postmortem examination was performed 2 hours after his death.

MATERIALS AND METHODS

Tissue specimens obtained from neck lymph node biopsy and autopsy were fixed in 10% formalin, and conventional 4 μm thick paraffin sections were prepared. The sections were used for routine histological observation with hematoxylin and eosin staining and for immunohistochemical analysis using a labeled streptavidin-biotin method. The primary antibodies employed in the present analysis are listed in Table 1. Briefly, deparaffinized tissue sections were immersed in either 0.1% trypsin (Difco, Franklin Lakes, NJ) in 0.01 M phosphate-buffered saline (PBS), pH7.4 with 0.15% $CaCl_2$ for 30 minutes at 37°C or in 1 mM ethylenediamine tetraacetic acid solution, pH8.0 (EDTA, Muto Pure Chemicals, Tokyo, Japan) microwaved (400W) for 24 minutes at 90°C for antigenic retrieval. Endogenous peroxidase activity was quenched with methanol containing 0.3% hydrogen peroxide and nonspecific antibody binding was blocked with protein-blocking agent or skim milk. The slides were then incubated at 4°C overnight with the relevant primary antibodies. The labeled streptavidin-biotin/horseradish peroxidase (LSAB/HRP) staining kit (DAKO, Glostrup, Denmark) was used. The reaction was developed with 3, 3′-diaminobenzidine (Dojin Chemicals, Kumamoto, Japan) as a brown color. The sections were counterstained with hematoxylin.

Formalin-fixed, paraffin-embedded sections of tonsils obtained from 3 patients with chronic tonsillitis and lymph nodes from 3 patients with reactive lymphadenitis were used as specificity controls for the antibodies. As a negative control, non-immune rabbit or mouse immunoglobulins were used instead of the primary antibodies. In addition, control procedures were performed to determine the reactivity of the biotinylated secondary antibodies and peroxidase-conjugated streptavidin and to quantify endogenous peroxidase activity.

RESULTS

Microscopic findings in biopsied lymph nodes

Biopsied neck LNs were markedly enlarged, and their normal architecture was completely effaced by diffuse infiltration of tumor cells (Fig. 1a & 1b). The morphology of the tumor cells was quite pleomorphic, frequently intermingled with a small number of non-neoplastic lymphocytes, plasma cells, eosinophils, and neutrophils. The majority of tumor

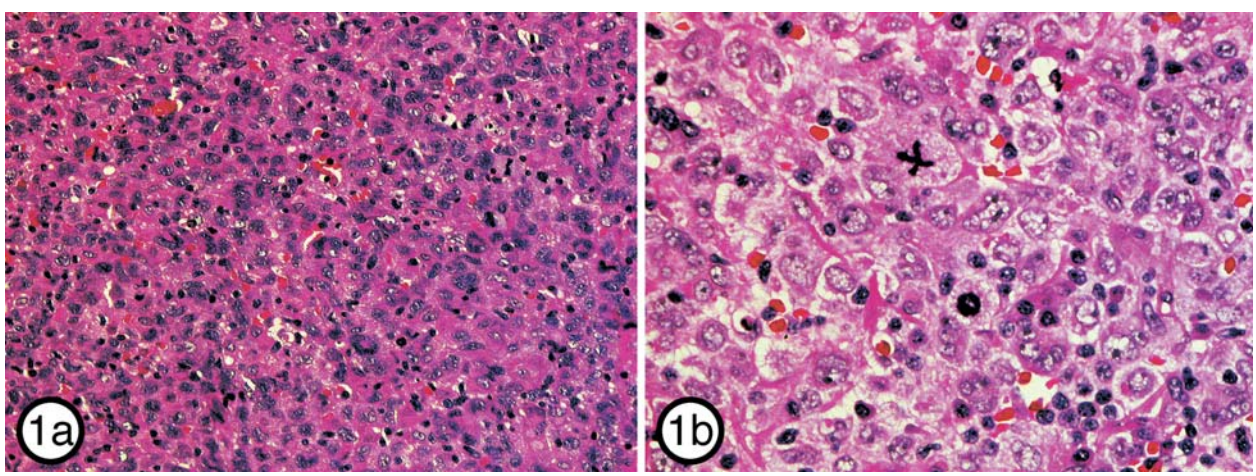

Fig. 1 Photomicrographs showing histological findings of tumor cells in the biopsied neck lymph node. (1a) Pleomorphic tumor cells diffusely proliferate with effacement of normal architecture. (1b) High-power view indicates abundant foamy cytoplasm and irregularly shaped nuclei with unusual lobulation of tumor cells. Atypical mitoses are frequently observed. 1a : hematoxylin-eosin (HE) staining, x20 (objective), 1b : HE staining, x40 (objective).

cells were large with abundant pale or slightly eosinophilic cytoplasm. The nuclei were generally bean-shaped with irregular indentation and contained a few, small to moderately large nucleoli. Some tumor cells with a highly lobulated nucleus or multinucleated cells, with ring-like-arranged nuclei, were also seen. The number of mitotic figures ranged from 20 to 24 per 10 high-power fields. Fibrosis was not evident in the area where diffuse neoplastic cells infiltrated, but a thin fibrous capsule partially surrounded the tumor nodules. Erythrophagocytosis of the tumor cells was rarely observed.

Immunohistochemically, the majority of tumor cells were positive for fascin (55K-2), S-100 protein, vimentin, and CD74 (LN2) (Fig. 2a-2c). CD68 (KP1)- and HLA-DR (LN3)-positive tumor cells were occasionally noted. No positive reactivity to CD1a (O10), CD3 (PS1), CD20 (L26), CD43 (DF-T1), or CD45 was observed. The MIB-1 (Ki-67) labeling index was 35 to 40%. The results of immunohistochemical labeling are summarized in Table 1.

Autopsy findings

At autopsy, marked hepatomegaly (3,100g) due to extensive tumor cell infiltration was seen (Fig. 3a & 3b). The tumor cells were highly pleomorphic and densely proliferating, predominantly in hepatic sinusoids. Splenomegaly (480g) was also detected with diffuse infiltration of pleomorphic tumor cells extending into the red pulp. In addition, tumor cells diffusely infiltrated into systemic LNs and bone marrow. The involved LNs were enlarged with complete effacement of the normal architecture, especially the mesenteric and retroperitoneal nodes which formed a conglomerated mass. Morphological and immunophenotypic features of tumor cells were similar to those in biopsied LNs. Skin involvement was not seen during his clinical course.

In spleen, bone marrow, and LNs, a large number of

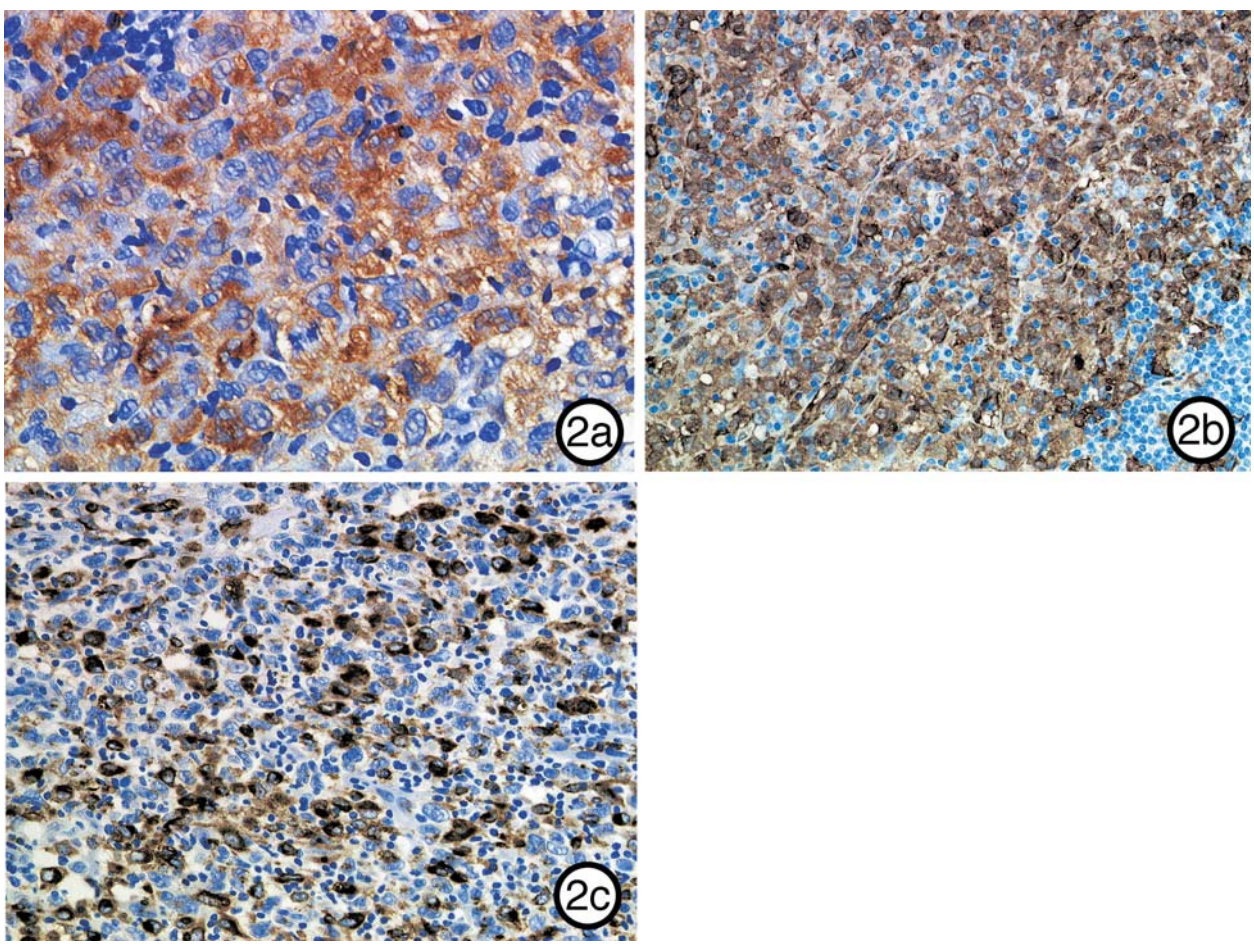

Fig. 2 Photomicrographs showing immunohistochemical findings of tumor cells in the biopsied neck lymph node. Most of the tumor cells reveal intense immunoreactivity of S-100 protein (2a) and fascin (2b). In addition, a portion displays obvious reactivity of KP-1/CD68 (2c). 2a-2c : Peroxidase labeled streptavidin-biotin labeling counterstained with hematoxylin, 2a : x40 (objective), 2b & 2c : x20 (objective).

Table 1. Immunohistochemical findings in this patient

Antibody (clone)	Source	Isotype	Reactivity of the tumor cells
CD1a (O10)	Immunotech	mouse IgG, κ	−
CD3 (PS1)	Nichirei	mouse IgG2a	−
CD5 (4C7)	Nichirei	mouse IgG1, κ	−
CD10 (56C6)	Nichirei	mouse IgG1	−
CD15 (C3D-1)	DAKO	mouse IgM, κ	−
CD20 (L26)	DAKO	mouse IgG2a, κ	−
CD21 (1F8)	DAKO	mouse IgG1, κ	−
CD23 (1B12)	Novocastra	mouse IgG1, κ	−
CD30 (BerH2)	DAKO	mouse IgG1, κ	−
CD35 (To5)	DAKO	mouse IgG1, κ	−
CD43 (DF-T1)	DAKO	mouse IgG1, κ	−
CD45 (2B11+PD7/26)	DAKO	mouse IgG1, κ	−
CD68 (KP-1)	DAKO	mouse IgG1, κ	+/−
CD74 (LN2)	DAKO	mouse IgG1, κ	+
Cytokeratin (AE1+AE3)	DAKO	mouse IgG1, κ	−
Desmin (D33)	DAKO	mouse IgG1, κ	−
Dendritic cell (DC-LAMP*)	Immunotech	mouse IgG1, κ	−
EMA (E9)	DAKO	mouse IgG2a, κ	−
Fascin (55K-2)	DAKO	mouse IgG1, κ	++
HLA-DR (LN3)	Nichirei	mouse IgG2a, κ	+/−
Melanoma (HMB-45)	DAKO	mouse IgG1, κ	−
Ki-67 antigen (MIB-1)	DAKO	mouse IgG1, κ	35~40%
Muscle actin (HHF35)	DAKO	mouse IgG1, κ	−
Myeloperoxidase	DAKO	rabbit polyclonal	−
S-100 protein	DAKO	rabbit polyclonal	+
Vimentin (V9)	DAKO	mouse IgG1, κ	++

* DC-LAMP ; Dendritic cell-lysosomal associated membrane protein

histiocytes, which had actively phagocytosed numerous erythrocytes, were seen among the tumor cells. These histiocytes were easily distinct from the tumor cells because they did not display nuclear atypia or immunoreactivity to the anti-S100 protein. This observation could be interpreted as evidence of reactive hemophagocytic syndrome (HPS).

DISCUSSION

Histiocytic and dendritic cell neoplasms are among the rarest of tumors affecting the hematopoietic and lymphoid tissues. The normal cellular counterparts of this group of neoplasms consist of two major subsets : antigen presenting cells or dendritic cells and antigen-processing cells or phagocytic cells. Most of these cells are derived from bone marrow hematopoietic stem cells and share a common cellular origin. However, antigen presenting cells and phagocytes are generally considered to represent two parallel and independent lines of differentiation. Langerhans cells (LC) and interdigitating cells (IDC) are representative dendritic cells (antigen presenting cells) which can present antigens to appropriate T-cells to promote differentiation or activation. LC are a type of immature dendritic cell, located primarily in the skin and defined by characteristic Birbeck granules in their cytoplasm and CD1a expression on their surface. IDC are mature dendritic cells with potent antigen presenting capacity distri-

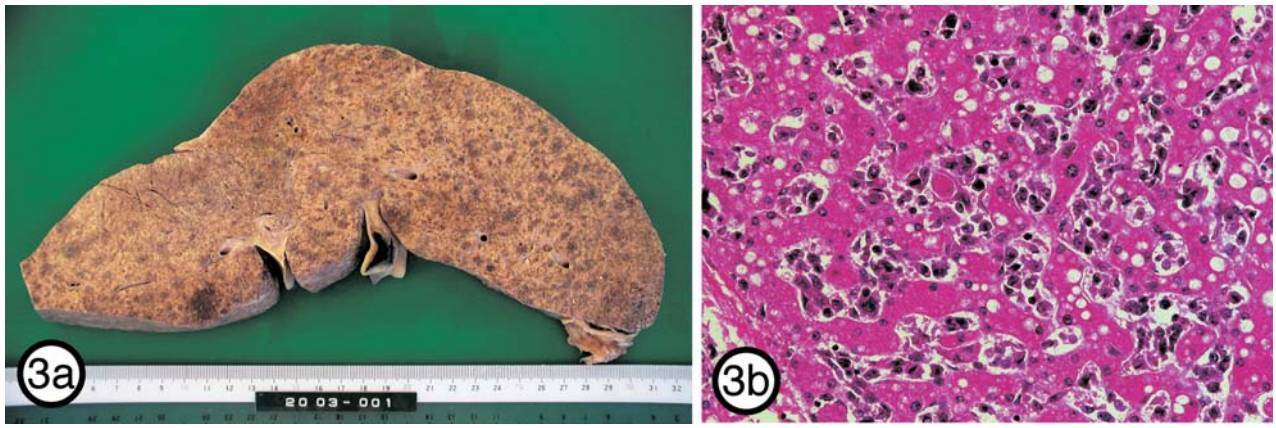

Fig. 3 A photograph showing gross appearance of the cut surface of the enlarged liver at autopsy (3a) and a photomicrograph showing microscopic features of the liver at autopsy (3b). Sinusoidal infiltration of the tumor cells is prominent. HE staining, x20 (objective).

buted in the T-cell areas of secondary lymphoid tissues. They have intense expression of MHC class II molecules and co-stimulatory molecules such as CD80, CD83, and CD86. Langerhans cell histiocytosis/sarcoma and IDC tumor/sarcoma are neoplastic counterparts of LC and IDC, respectively, and are defined as distinct clinicopathological entities[31]. In contrast, histiocytes or mononuclear phagocytes primarily function in the removal of particulate antigens, dead cells, and cellular waste and are thought to be derived from the circulating blood monocyte pool. Histiocytic sarcoma or malignant histiocytosis is neoplastic counterparts of mononuclear phagocytes. Therefore, tumor cells show morphologic and immunophenotypic features similar to those of mature tissue histiocytes. As a result, they occasionally reveal phagocytic activity and express "histiocytic markers including CD68, lysozyme, CD11c, and CD14[31].

In the present case, the normal architectures of both of the biopsied neck LNs and systemic LNs from autopsy were completely effaced by a diffuse proliferation of tumor cells. Pleomorphic histiocyte-like tumor cells, including multinucleated giant cells, diffusely proliferated intermingled with a small number of non-neoplastic lymphocytes, plasma cells, eosinophils, and neutrophils. At autopsy, tumor cells widely involved the liver, spleen, bone marrow, peripheral blood, and systemic LNs. The tumor cell immunophenotype (S-100 protein^{+}, CD68$^{+/-}$, HLA-DR^{+}, fascin^{+}, vimentin^{+}, cytokeratin^{-}, and CD30^{-}) was identical with that of previously reported neoplastic IDCs[25,31]. Taken together with clinical and histopathological findings, the present tumor was compatible with IDC sarcoma arising from his neck or para-aortic LNs. The vast majority of the tumor cells were clearly positive for fascin, which is particularly important for identifying IDC or its neoplastic counterpart. Although expression of CD1a is variable among published cases of IDC sarcoma, the tumor cells in this patient did not display significant expression of the molecule[25,31].

In this patient, significantly elevated serum sIL-2R was recognized. The serum concentration of sIL-2R is frequently increased not only in patients with malignant lymphoma[33], but also in other tumors including lung[34], ovarian[35], colonic[36] and esophageal carcinomas[37]. Recently, several reports[35,37] indicated that tumor cells can produce sIL-2R, even in non-lymphoid neoplasms. If specific antibodies or probes were available, further analysis would be expected to define which cells produce this receptor in the present case.

As described in the autopsy findings, numerous histiocytic cells, showing active phagocytosis of erythrocytes and other leukocytes, were observed among the tumor cells in lymph nodes, spleen, and bone marrow. These cells seemed to be reactive histiocytes rather than tumor cells because they obviously lacked nuclear atypia and reactivity to anti-S100 antibody, whereas they expressed intense CD68 reactivity. These findings indicated that reactive HPS complicated the IDC sarcoma at the terminal period of the disease. Thus far, although HPS has been described as associated with different types of neoplasms including T/NK-cell lymphoma[38], B-cell lymphoma[39], acute myeloid leukemia[40], multiple myeloma[41], and hepatocellular carcinoma[42], there have been no reports on IDC sarcoma or related neoplasms accompanied by HPS.

To date, 42 cases of IDC sarcoma (Table 2) have been reported in the English literature, including our case. The clinicopathological features of these patients can be summarized as follows : 1) age ranged from 6 to 87 years, with an average of 48.74 years and a median of 55 years ; 2) lymph node-based diseases were frequent, while disease rarely arised from the spleen, skin, intestine, and oro-nasopharynx ; 3) secondary involvement of tumor cells in liver, bone marrow, and lungs was frequent. In 30 cases of IDC sarcoma with survival data, the average survival was 22.66 months and the median was 9.5 months (Table 2). Among these cases,

Table 2. Previous case reports of interdigitating cell sarcoma

Author	Sex/Age	Involved Sites	Treatment	Survival	Reference
Lennert & Mohri	F/69	LNs	not described	−	4
Feltkamp	M/37	LNs, Skin, Mediastinum	CT	4 M	5
Turner et al.	M/17	LNs, Spleen, Liver	CT	.M	6
	M/30	Nasopharynx	RT	>2.M	
Daum et al.	M/43	Jejunum, Mesentery	CT+SG	.M	7
Salisbury et al.	F/41	LNs	CT+AutoBMT	>.M	8
Chan & Zaatari	M/67	LNs, Spleen, Liver, Lungs	CT	.W	9
van den Oord et al.	F/74	Axillary LN, Mediastinum	RT	−	10
Nakamura et al.	M/58	LNs, Jejunum	CT+SG+RT	>6.M	11
Hui et al.	M/67	Skin	not described	7.M	12
Rabkin et al.	M/17	LNs, Spleen, BM	CT+SG	.M	13
	F/13	LNs, Spleen, Media-stinum, Ovaries	CT+RT	.M	
Weiss et al.	M/60	Supraclavicular LN	SG+RT	>1.M	14
	M/34	LNs, BM, Skin, Liver, Lung, Heart	CT+SG+AutoBMT	1.M	
Yamakawa et al.	M/54	LNs, Pleural effusion	CT	1.M	15
Hammar et al.	M/67	Neck LN	SG	>4.M	16
Horschowski et al.	M/8	LNs, Colomesentery	CT	.M	17
Miettinen et al.	F/52	LNs, Small intestine, Abdominal masses	CT	1.M	18
	M/58	Ileum, Liver, Mesentery	CT+SG	>1.M	
Rousselet et al.	F/20	LNs	CT+RT	>1.M	19
Vasef et al.	F/56	LNs	CT	−	20
Andriko et al.	M/23	LNs	SG+RT	>4.M	21
	F/32	Neck LN	SG	−	
Banner et al.	F/68	LNs, Cecum	CT	−	22
Luk et al.	M/74	Right testis	SG	>.M	23
Gaertner et al.	M/61	LNs, Lung, Chest wall, Spleen	CT	>1.M	24
	M/70	Axillary LN	SG	>.M	
	F/77	Tonsil	RT	>.M	
	F/73	LNs with organ metastasis	SG	.M	
Pileri et al.	M/60	Skin (multiple nodules)	CT	−	25
	F/78	Inguinar LN	SG+RT	−	
	F/83	Axillary LN	not described	−	
	M/67	Neck LN	not described	−	
Kawachi et al.	F/87	Spleen	SG	.M	26
Olnes et al.	F/44	LNs	CT	−	27
Barwell et al.	F/51	Salivary gland	SG	−	28
Martins et al.	F/50	Oral cavity	SG	−	29
Pillay et al	F/6	Intrapelvic mass	CT+SG	4..M	30
	F/10	Chest wall	SG	>12.M	
	F/12	Vertebral bone	CT+SG+RT	>10.M	
	M/21	LNs, Spleen, Liver, PB	CT	2.M	
The present case	M/58	LNs, Liver, Spleen, BM	CT	.M	

Abbreviations ; LNs : lymph nodes, BM : bone marrow, PB : peripheral blood, CT : chemotherapy, SG : surgery, RT : radiation therapy, BMT : bone marrow transplantation, − : no available data

63.33% died within one year of disease onset, and 30% of cases died within 6 months. These data reveal that IDC sarcoma has the characteristics of a high-grade malignancy[43]. The following features of the present case may be predictive of an aggressive nature : 1) relatively early in the clinical period, the patient exhibited extensive involvement of tumor cells in the bone marrow, spleen, and liver, as well as systemic lymph nodes ; 2) histologically, the mitotic frequency (2 to 2.4/high power fields) and MIB-1 (Ki-67) labeling index (35- 40%) were very high ; 3) complications from hemophagocytosis may hasten death[26].

Although rare cases of IDC sarcoma have been reported to be responsive to ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy[27], there exists no consensus on a standard chemotherapeutic regimen for this type of tumor. Most patients with this malignancy have been treated with chemotherapeutic regimens against non-Hodgkin's lymphomas. Responses to these regimens have been variable, but mostly unsuccessful. The different clinicopathological features of IDC sarcoma are not fully understood, but when individual cases are gathered and their clinicopathological characteristics are precisely analyzed in the future, useful information regarding the degree of biological aggressiveness and applicable treatment for this malignancy should be provided.

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