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**Inflammatory pseudotumor-like follicular dendritic cell sarcoma: Literature review of 67 cases**

Wu H *et al.* Inflammatory pseudotumor-like follicular dendritic cell sarcoma

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**Abstract**

Inflammatory pseudotumor (IPT)-like follicular dendritic cell (FDC) sarcoma is rare. The 2017 World Health Organization classification of tumors of hematopoietic and lymphoid tissues noted that data on its clinical outcome are limited, but that the tumor appears to be indolent. The aim of this study was to summarize the clinical characteristics, treatment outcomes, and prognostic factors for IPT-like FDC sarcoma. A literature review was conducted on retrospective analyses of clinical data and prognostic information on IPT-like FDC sarcoma reported between 2001 and 2020. A total of 67 cases of IPT-like FDC sarcoma were retrieved from the literature, documenting that it occurs predominantly in middle-aged adults, with a marked female predilection. Six patients had a separate malignancy and five had an autoimmune disease. Typically involving the spleen and/or liver, it may also selectively involve the abdomen, gastrointestinal tract, pancreas, retroperitoneum, and mesentery. Necrosis, hemorrhage, noncaseating epithelioid granulomas, and fibrinoid deposits in blood vessel walls are often present. The neoplastic cells are predominantly positive for follicular dendritic cell markers such as cluster of differentiation 21 (CD21), CD23, CD35 and CNA.42 and are consistently Epstein-Barr virus (EBV)-positive. Mitoses were very rare in most cases. Most patients were treated by surgery alone. Disease status at the time of last follow-up was known for 57 patients with follow-up time ranging from 2 to 144 mo. Local and/or distant recurrence after initial treatment was seen in 15.8% of the patients. The 1- and 5-year progression-free survival for the entire group was 91.5% and 56.1%, respectively. Kaplan-Meier and multivariate analyses showed that age, sex, tumor size, and pathological features were not risk factors for disease progression. IPT-like FDC sarcoma appears to be mildly aggressive and requires annual surveillance. Surgery is the most effective treatment modality, and the role of adjuvant chemotherapy for postoperative management is unclear. EBV is likely to play an important role in the etiology of IPT-like FDC sarcoma.

**Key Words:** Inflammatory pseudotumor-like; Follicular dendritic cell sarcoma; Spleen; Liver; Prognosis; Epstein-Barr virus

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**Core Tip:** We show that inflammatory pseudotumor-like follicular dendritic cell (FDC) sarcoma appears to be mildly aggressive and does require annual surveillance. Surgery is the most effective treatment modality, and the role of adjuvant chemotherapy for postoperative management is unclear. Epstein-Barr virus is likely to play an important role in the etiology of inflammatory pseudotumor-like FDC sarcoma.

**INTRODUCTION**

Follicular dendritic cells (FDCs) develop from perivascular precursors of stromal cell origin that are seeded throughout the body. They are centrally located within B cell follicles and act as a bridge between innate and adaptive responses[1]. Monda *et al*[2] first reported 4 cases of tumors derived from FDC in 1986. FDC sarcoma is an uncommon neoplasm that can involve lymph nodes or extranodal sites. It usually has an aggressive course in the abdomen[3]. Cheuk *et al*[4] first characterized inflammatory pseudotumor(IPT)-like FDC sarcoma as an EBV-associated tumor of FDC origin in 2001. The most recent World Health Organization (WHO) classification noted that IPT-like FDC sarcoma appears to be indolent and that data on clinical outcome are limited[5].

In this study, we detail the features of 67 cases with IPT-like FDC sarcoma, providing an overview of the current knowledge about the clinical, pathological, and prognostic characteristics of this disease entity.

**LITERATURE REVIEW**

We systematically searched PubMed, EMBASE, and MEDLINE databases using the search terms “inflammatory pseudotumor-like” combined with “follicular dendritic cell sarcoma” or “follicular dendritic cell tumor” or “fibroblastic dendritic cell sarcoma” or “fibroblastic dendritic cell tumor” and with the restrictions “English” language and “original article.” We collated demographic, clinicopathological and follow-up information.

All statistical analyses were performed using SPSS Statistics 25.0 software (IBM Corporation, Armonk, NY, United States). Survival curves were replotted with Graphpad prism 8.0 software (Graphpad Inc., La Jolla, CA, United States). *P* < 0.05 was considered statistically significant, and variables pertaining to accuracy were calculated with 95% confidence intervals.

**PATIENT CHARACTERISTICS**

Data on a total of 67 cases of IPT-like FDC sarcoma were retrieved from the literature. Patients and disease characteristics are summarized in Table 1. The median age at initial presentation was 53 years (range: 19-79). Females were more commonly affected than males (*n* = 42 *vs* 25). Patients were asymptomatic or presented with abdominal distension or pain, sometimes accompanied by systemic symptoms such as fever, fatigue, and weight loss. Other cancers were observed in 6 patients before their diagnosis with IPT-like FDC sarcoma including gastric cancer (*n* = 3), breast cancer (*n* = 1), pituitary adenoma, meningioma, and acoustic neuroma (*n* = 1) and diffuse large B-cell lymphoma (*n* = 1). Five patients (7.5%) had pre-existing or subsequent autoimmune disease including pemphigus and bronchiolitis obliterans (*n* = 1), IgA nephropathy (*n* = 1), nephrotic syndrome (*n* = 1), bronchial asthma (*n* = 1), and idiopathic thrombocytopenic purpura (*n* = 1).

**DISEASE CHARACTERISTICS**

Thirty-five patients (52.2%) presented solely with spleen involvement and twenty (29.9%) only with liver. For the remaining patients, lesion sites included the abdomen (*n* = 1), colon (*n* = 4), spleen and pancreas (*n* = 1), retroperitoneum (*n* = 1), ileum and mesentery (*n* = 1), liver and hepatoduodenal ligament lymph node (*n* = 1), spleen and liver (*n* = 2) and peri-pancreas (*n* = 1). The average size of tumors at all sites was 7.6 cm, ranging from 0.9 to 23.3 cm (median, 6.2 cm). Bulky tumor (≥ 5 cm) was noted in 43 patients (64.2%). Seven patients presented with more than one lesion. The radiologic findings of IPT-like FDC sarcoma have been described in several cases. The abdominal computed tomography scan showed a well-circumscribed or ill-defined, hypodense mass with weak delayed heterogeneous enhancement after contrast enhancement in the spleen or liver. Some of these lesions reveal irregular areas of nonenhancement related to foci of tumoral necrosis and hemorrhage.

**PATHOLOGICAL FEATURES**

The pathological features are summarized in Table 2. In all, 40 cases (59.7%) presented with necrosis, 22 (32.8%) with hemorrhage, 23 (34.3%) with noncaseating epithelioid granulomas and 22 (32.8%) with fibrinoid deposits in the blood vessel wall. The neoplastic cells were predominantly positive for the follicular dendritic cell markers CD21(54/65), CD23 (34/47), CD35 (50/55) and CNA.42 (13/13). Tumor cells were usually positive for clusterin (8/11), vimentin (6/6), fascin (9/9), and smooth muscle actin (32/39), and variably positive for S100 (6/23), D2-40 (6/10), epidermal growth factor receptor (3/8), muscle-specific actin (5/9), epithelial membrane antigen (2/8), CD68 (8/16), tubulin beta 3 class III (3/6) andγ-synuclein (2/6). There was no staining for CD117, cytokeratin, caldesmon, activin-like kinase 1 (ALK1), desmin or human herpes virus 8 (HHV8). In 4 cases, the tumor cells resembled Reed-Sternberg cells. The neoplastic cells were consistently associated with EBV, and EBV-encoded small RNA (EBER) was positive in 60 cases (95.2%) by *in situ* hybridization. Immunoreactivity for EBV-encoded latent membrane protein 1 (LMP1) was present in 28 cases (82.4%). One case present with *LMP1* gene fragment deletions and point mutations. Increased IgG4-postive plasma cells were found in 6 cases. Mitoses were very rare in most cases and the Ki-67 proliferation index ranged from 3% to 30%.

**TREATMENT INFORMATION**

Information on treatment was available for all 67 patients, most of whom (65/67) underwent surgery alone. Only 2 patients received surgery and chemotherapy (one with two cycles of cyclophosphamide, doxorubicin, vincristine and prednisone, and the other with CHOP-based chemotherapy).

**PATIENT OUTCOMES**

Disease status at the time of last follow-up was known for 57 of the 67 patients; these patients were eligible for progression-free survival (PFS) analyses. The follow-up time ranged from 2 to 144 mo (mean, 22 mo; median, 12 mo). Overall, 9 of the 57 (15.8%) had local and/or distant recurrence after initial treatment. Two patients died due to disease progression, but two others had no evidence of disease after undergoing a second surgery. The 1- and 5-year PFS for the entire group was 91.5% and 56.1%, respectively (Figure 1). Young age, male sex, and large tumor size may contribute to less disease progression. However, Kaplan-Meier and multivariate analyses failed to confirm that age, sex, tumor size or and pathological features are risk factors for disease progression (Table 3).

**DISCUSSION**

In 1986 Monda *et al*[2] first reported 4 cases of tumors derived from FDC and in 2001 Cheuk *et al*[4] reported that IPT-like FDC sarcoma were EBV-associated tumors of FDC origin. Currently, FDC sarcomas are classified into conventional and IPT-like FDC sarcoma[5]. Our study indicated that IPT-like FDC sarcoma occurs predominantly in middle-aged adults, with a marked female predilection unlike the equal distribution between the sexes of conventional FDC sarcoma. IPT-like FDC sarcoma typically involves the spleen and/or liver. Genetic lineage-tracing approaches show that FDC develop from splenopancreatic embryonic mesenchymal cells of the Nkx2-5(+) Islet1(+) lineage[6]. FDC emerge from perivascular precursors, engaging B cells in germinal centers of secondary lymphoid organs[1,7]. Our analysis indicated that 7.7% patients had pre-existing or subsequent autoimmune disease. Conventional FDC sarcoma also showed a trend for occurring coincidentally with autoimmune disease[3]. FDC can retain antigens to establish contact with B cells, and secrete milk-fat globule epidermal growth factor 8, which controls the engulfment of apoptotic B cells by macrophages. Excessive accumulation of apoptotic B cells may result in lupus-like autoimmunity[8,9]. Furthermore, FDC was shown to be important for the retention of self-antigen-containing immune complexes in a spontaneous arthritis model[10].

We found that the average size of tumors was 7.6 cm, ranging from 0.9 to 23.3 cm (median, 6.2 cm). Bulky tumor (≥ 5 cm) was noted in 43 patients. Necrosis, hemorrhage, noncaseating epithelioid granulomas, and fibrinoid deposits in blood vessel walls are often present in IPT-like FDC sarcoma. A pooled analysis demonstrated that young age, large tumor size and coagulative necrosis may predict poor prognosis in conventional FDC sarcoma[11], but our data failed to demonstrate that age, large tumor size, and necrosis are risk factors for disease progression in IPT-like FDC sarcoma. The neoplastic spindle-shaped cells of the latter are present within a prominent lymphoplasmacytic infiltrate and may even resemble Reed-Sternberg cells[4,12]. IPTs can also be found in the spleen and liver, and tend to appear as plump spindle cells in a polymorphic inflammatory cell infiltrate[13,14]. IPT-like FDC sarcomas are predominantly positive for the FDC markers CD21, CD23, CD35 and CNA.42, thus distinguishing them from Hodgkin lymphoma and IPTs. Moreover, IPT-like FDC sarcomas are negative for cytokeratin, CD117, caldesmon, ALK1, desmin and HHV8, which can help in the differential diagnosis of epithelial carcinoma, gastrointestinal stromal tumor, inflammatory myofibroblastic tumor, anaplastic large cell lymphoma, rhabdomyosarcoma and Kaposi sarcoma. IPT-like FDC sarcomas are usually positive for clusterin, vimentin and fascin. Strong clusterin staining appears to be a highly sensitive marker of FDC sarcoma. Vimentin staining may confirm mesenchymal origin, but is relatively nonspecific. Fascin staining was not specific for spindle cell tumors and thus does not imply a dendritic cell lineage[15,16].

Our study concluded that 95.2% of patients possessed tumor cells positive for EBER by *in situ* hybridization, and 82.4% were immunoreactive for EBV-encoded LMP1. EBV has a long history of coevolution with humans. The result is a finely balanced relationship that usually allows the virus to be carried as a lifelong asymptomatic infection. However, the pathogenic potential of EBV has been confirmed in several autoimmune disorders, particularly multiple sclerosis, and a wide range of human tumors[17]. Approximately 2.2 million cases of cancers in 2018 were attributable to infectious agents. It is estimated that EBV accounts for more than 150000 of these, mainly nasopharyngeal carcinomas, Hodgkin lymphomas and Burkitt lymphomas[18]. IPT-like FDC sarcoma cells were consistently positive for EBER and LMP1. Interestingly, increased IgG4-postive plasma cells were found in 6 cases[19]. There is evidence for the presence of increased numbers of EBV-infected cells in IgG4-related lymphadenopathy[20]. EBV lytic reactivation induces IgG4 production in Graves’ disease[21]. The etiology of EBV in IPT-like FDC sarcoma needs further research.

Surgery is the most effective therapy for IPT-like FDC sarcoma, and the number of cases treated by adjuvant chemotherapy is limited. Nevertheless, here we saw that 15.8% patients had local and/or distant recurrence after initial treatment. The WHO has noted that data on clinical outcomes are limited, but that the tumor appears to be indolent[5]. Our research revealed that 1- and 5-year PFS for the entire group was 91.5% and 56.1%, respectively.

**CONCLUSION**

There is a certain risk of relapse after the initial therapy of IPT-like FDC sarcoma, which therefore needs annual surveillance. Surgery is the most effective treatment modality, and the role of adjuvant chemotherapy for the management of postoperative is not clear. EBV plays an important role in the etiology of IPT-like FDC sarcoma.

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**Footnotes**

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**Figure Legends**



**Figure 1 Progression-free survival curve for patients with inflammatory pseudotumor-like follicular dendritic cell sarcoma.**

**Table 1 Clinical characteristics of patients with inflammatory pseudotumor-like follicular dendritic cell sarcoma**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case No.**  | **Ref.** | **Sex/age** | **Site** | **Maximum diameter in cm** | **Symptom** | **Treatment** | **Time to recurrence in mo** | **Last follow-up in mo** | **Outcome**  |
| 1 | Rao *et al*[22] | 39/M | Spleen | 7.2 | Asymptomatic | Surgery | NA | NA | NA |
| 2 | Zhao[23] | 28/F | Abdomen | 9 | Skin rash, cough | Surgery | NA | NA | NA |
| 3 | Kazemimood *et al*[12] | 53/F | Colon | 3 | Abdominal discomfort | Surgery | NA | NA | NA |
| 4 | Hommel *et al*[24] | 77/F | Spleen | 12 | Left upper quadrant abdominal pain | Surgery | - | 4 | NED |
| 5 | Hang *et al*[25] | 57/M | Spleen | 2.7 | Asymptomatic | Surgery | - | 9 | NED |
| 6 | Granados *et al*[26] | 57/F | Liver | 13 | Abdominal pain, vomiting | Surgery | - | 24 | NED |
| 7 | Kiryu *et al*[27] | 56/F | Spleen | 4 | Asymptomatic | Surgery | - | 24 | NED |
| 8 | Li *et al*[28] | 32/F | Liver | 3 | - | Surgery | - | 8 | NED |
| 9 | Pan *et al*[29] | 78/F | Colon | 3.9 | Abdominal discomfort, bloody stool | Surgery | - | 5 | NED |
| 10 | Ang *et al*[30] | 63/F | Liver | 13.4 | Fever and lethargy | Surgery | - | 48 | NED |
| 11 | Wu *et al*[31] | 45/M | Liver | 8 | Abdominal pain and weight loss | Surgery | - | 9 | NED |
| 12 | Zhang *et al*[32] | 19/F | Liver | 6 | Abdominal discomfort | Surgery | - | 12 | NED |
| 13 | Deng *et al*[33] | 67/F | Liver | 4 | Cough | Surgery | NA | NA | NA |
| 14 | Horiguchi *et al*[34] | 77/F | Spleen | 8.5 | Epigastralgia | Surgery | - | 36 | NED |
| 15 | Kitamura *et al*[35] | 74/F | Spleen | 3.6 | Asymptomatic | Surgery | - | 24 | NED |
| 16 | Kim *et al*[36] | 76/M | Spleen | 3.2 | Asymptomatic | Surgery | - | 7 | NED |
| 17 | Kwon[37] | 58/F | Spleen | 5 | Asymptomatic | Surgery | - | 24 | NED |
| 18 | Nishiyama *et al*[38] | 73/F | Spleen | 8 | Asymptomatic | Surgery | - | 144 | NED |
| 19 | Bui *et al*[39] | 50/F | Spleen | 8.5 | Abdominal pain | Surgery | NA | NA | NA |
| 20 | Mograbi *et al*[40] | 70/F | Spleen, Pancreas | Spleen: 3,Pancreas: 7 | Asymptomatic | Surgery | NA | NA | NA |
| 21 | Hu *et al*[41] | 49/F | Retroperitoneum | 5 | Asymptomatic | Surgery | Tail of pancreas (60) | 60 | NED |
| 22 | Vardas *et al*[42] | 61/M | Spleen | 10 | Abdominal pain | Surgery | - | 12 | NED |
| 23 | Agaimy *et al*[43] | 52/M | Ileum and mesentery | 6 | Abdominal pain | Surgery | NA | NA | NA |
| 24 | Ge *et al*[44] | 54/F | Spleen | 3.5 | Left upper quadrant abdominal pain | Surgery | - | 10 | NED |
| 25 | Ge *et al*[44] | 79/M | Spleen | 6 | Asymptomatic | Surgery | - | 18 | NED |
| 26 | Zhang *et al*[45] | 31/F | Liver | 2 masses: 3.5, 2.5 | Anorexia | Surgery | - | 10 | NED |
| 27 | Zhang *et al*[45] | 48/M | Liver and hepatoduodenal ligament lymph node | Liver: 10, Lymph: 3.5 | Asymptomatic | Surgery | - | 2 | NED |
| 28 | Ke *et al*[46] | 53/M | Colon | 1 | Chest and back pain | ESD | - | 11 | NED |
| 29 | Ke *et al*[46] | 48/M | Colon | 4.5 | Left lower quadrant pain | Surgery | - | 7 | NED |
| 30 | Li *et al*[47] | 64/F | Spleen | 7.2 | Upper abdominal pain | Surgery | - | 8 | NED |
| 31 | Li *et al*[47] | 61/M | Spleen | 6.2 | Asymptomatic | Surgery | - | 16 | NED |
| 32 | Li *et al*[47] | 42/F | Spleen | 4 | Left-sided flank pain | Surgery | - | 9 | NED |
| 33 | Li *et al*[47] | 57/F | Spleen | 13.3 | Upper abdominal pain | Surgery | Pulmonary (4) | 4 | LWD |
| 34 | Li *et al*[47] | 52/M | Spleen | 2.9, 3.7 | Back pain | Surgery, chemotherapy | Multiple bone (5) | 5 | LWD |
| 35 | Li *et al*[48] | 49/F | Spleen | 4.7 | Asymptomatic | Surgery | - | NA | NA |
| 36 | Li *et al*[48] | 56/F | Spleen | 8 | Abdominal pain | Surgery | - | 17 | NED |
| 37 | Li *et al*[48] | 38/M | Liver | 8.5 | Fatigue, anorexia | Surgery | - | 11 | NED |
| 38 | Li *et al*[48] | 42/F | Liver | 2, 1.7 | Abdominal pain | Surgery | - | 36 | NED |
| 39 | Li *et al*[48] | 50/M | Spleen and liver | Spleen: 10, Liver: 3, 1.5, 1 | Abdominal bloating, fatigue | Surgery | - | 17 | NED |
| 40 | Li *et al*[48] | 39/F | Liver | 9 | Asymptomatic | Surgery, chemotherapy | Liver (12) | 84 | NED |
| 41 | Choe *et al*[19] | 64/F | Spleen | 5.5 | Asymptomatic | Surgery | - | 78 | NED |
| 42 | Choe *et al*[19] | 72/F | Spleen | 7.2 | Asymptomatic | Surgery | - | 18 | NED |
| 43 | Choe *et al*[19] | 53/F | Spleen | 3.2 | Asymptomatic | Surgery | - | 13 | NED |
| 44 | Choe *et al*[19] | 76/M | Spleen | 3.2 | Asymptomatic | Surgery | - | 8 | NED |
| 45 | Choe *et al*[19] | 72/M | Spleen | 6 | Asymptomatic | Surgery | - | 18 | NED |
| 46 | Choe *et al*[19] | 75/M | Spleen | 3.5 | Abdominal pain | Surgery | - | 30 | NED |
| 47 | Chen *et al*[49] | 28/F | Liver | 6 | Abdominal pain, fatigue, anorexia | Surgery | Liver (48) | 48 | LWD |
| 48 | Chen *et al*[49] | 39/M | Spleen | 7.4 | Asymptomatic | Surgery | - | 40 | NED |
| 49 | Chen *et al*[49] | 48/M | Liver | 23.3 | Abdominal pain, fever, fatigue | Surgery | - | 23 | NED |
| 50 | Chen *et al*[49] | 65/M | Spleen and liver | Spleen: 22.3, Liver: Multiple masses (largest: 5.8) | Abdominal pain, fever, fatigue, anorexia, weight loss | Surgery | - | 2 | DOD |
| 51 | Chen *et al*[49] | 51/M | Spleen | 8.5 | Weight loss | Surgery | - | 19 | NED |
| 52 | Chen *et al*[49] | 68/M | Spleen | 2.3 | Asymptomatic | Surgery | - | 6 | NED |
| 53 | Chen *et al*[49] | 51/F | Spleen | 5.3 | Epigastric discomfort | Surgery | - | 5 | NED |
| 54 | Chen *et al*[49] | 67/M | Spleen | 7.5 | Asymptomatic | Surgery | - | 5 | NED |
| 55 | Chen *et al*[49] | 60/M | Liver | 3 | Asymptomatic | Surgery | - | 3 | NED |
| 56 | Chen *et al*[49] | 52/F | Spleen | 0.9 | Asymptomatic | Surgery | - | 12 | NED |
| 57 | Cheuk *et al*[4] | 19/F | Liver | 12 | Right upper quadrant pain, weight loss | Surgery | - | 40 | NED |
| 58 | Cheuk *et al*[4] | 56/F | Liver | 15 | Abdominal discomfort | Surgery | Liver (15, 27 ,35) | 56 | LWD |
| 59 | Cheuk *et al*[4] | 40/F | Liver | 12.5 | Abdominal pain, weight loss | Surgery | Intraabdominal (108) | 108 | LWD |
| 60 | Cheuk *et al*[4] | 49/F | Liver | 4.2 | Asymptomatic | Surgery | - | 9 | NED |
| 61 | Cheuk *et al*[4] | 37/M | Liver | 15 | Weight loss | Surgery | - | 42 | NED |
| 62 | Cheuk *et al*[4] | 35/F | Liver | 20 | Abdominal discomfort, fever, weight loss | Surgery | Liver (30, 40), peritoneum and ascending colon (60) | 95 | DOD |
| 63 | Cheuk *et al*[4] | 31/F | Liver | 15 | Abdominal distension, weight loss | Surgery | - | 60 | NED |
| 64 | Cheuk *et al*[4] | 58/F | Spleen | 22 | Abdominal distension | Surgery | - | 4 | NED |
| 65 | Cheuk *et al*[4] | 39/F | Spleen | 7.5 | Weight loss, fever | Surgery | - | 2 | NED |
| 66 | Cheuk *et al*[4] | 61/F | Spleen | 3.5 | Asymptomatic | Surgery | NA | NA | NA |
| 67 | Cheuk *et al*[4] | 49/F | Peri-pancreas | 9.5 | Abdominal distension | Surgery | NA | NA | NA |

 DOD: Dead of disease; ESD: Endoscopic submucosal dissection; LWD: Live with disease; NA: Not available; NED: No evidence of disease.

**Table 2 Pathological features of inflammatory pseudotumor-like follicular dendritic cell sarcoma**

|  |  |  |
| --- | --- | --- |
| **Markers** | **Number of cases positive/number of cases tested** | **Cases positive, %** |
| Necrosis | 40/67 | 59.7 |
| Hemorrhage | 22/67 | 32.8 |
| Granuloma | 23/67 | 34.3 |
| Fibrinoid deposits in blood vessel wall | 22/67 | 32.8 |
| CD1a | 0/6 | 0 |
| CD3 | 0/7 | 0 |
| CD20 | 1/9 | 11.1 |
| CD21 | 54/65 | 83.1 |
| CD23 | 34/47 | 72.3 |
| CD30 | 1/27 | 3.7 |
| CD31 | 1/8 | 12.5 |
| CD34 | 5/15 | 33.3 |
| CD35 | 50/55 | 90.9 |
| CD68 | 8/16 | 50 |
| CD117 | 0/9 | 0 |
| LMP1 | 28/34 | 82.4 |
| EBER | 60/63 | 95.2 |
| D2-40 | 6/10 | 60 |
| CNA.42 | 13/13 | 100 |
| Clusterin | 8/11 | 72.7 |
| EGFR | 3/8 | 37.5 |
| Vimentin | 6/6 | 100 |
| CK-pan | 0/9 | 0 |
| Caldesmon | 0/7 | 0 |
| ALK1 | 0/42 | 0 |
| Desmin | 0/30 | 0 |
| Fascin | 9/9 | 100 |
| SMA | 32/39 | 82.1 |
| MSA | 5/9 | 55.5 |
| EMA | 2/8 | 25 |
| S100 | 6/23 | 26.1 |
| p53 | 1/6 | 16.7 |
| HHV-8 | 0/7 | 0 |
| TUBB3 | 3/6 | 50 |
| γ-synuclein | 2/6 | 33.3 |

EMA: Epithelial membrane antigen; HHV-8: Human herpes virus 8; LMP1: Latent membrane protein 1; MSA: Muscle-specific actin; SMA: Smooth muscle actin; TUBB3: Tubulin beta 3 class III.

**Table 3** **Factors evaluated by univariate and multivariate for association with progression-free survival**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Univariate analysis** | **Multivariate analysis** |
| ***P* value** | **HR (95%CI)** | ***P* value** | **HR (95%CI)** |
| Age ≤ 40 yr | 0.50 | 1.55 (0.39-6.16) | 0.48 | 1.78 (0.36-8.77) |
| Gender, male/female | 0.97 | 0.97 (0.21-4.64) | 0.67 | 1.51 (0.23-10.04) |
| Tumor size < 5 cm | 0.59 | 0.59 (0.11-3.32) | 0.43 | 0.38 (0.04-4.10) |
| Necrosis  | 0.31 | 0.51 (0.10-2.59) | 0.24 | 0.25 (0.03-2.49) |
| Hemorrhage  | 0.99 | 0.99 (0.27-3.70) | 0.84 | 1.25 (0.13-11.91) |
| Granuloma | 0.58 | 0.66 (0.16-2.71) | 0.85 | 0.84 (0.14-5.15) |

HR: Hazard ratio; CI: Confidence interval.



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