Case Series

CASTLEMAN DISEASE IN CHILDREN: DIAGNOSIS AND TREATMENT

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ABSTRACT

Background: *We describe the experiences in diagnosis and results of treatment in pediatric Castleman disease.*

Method: *Serial case reports.*

Result: *From 2016 to 2019, we had 7 cases of pediatric Castleman disease: 3 boys and 4 girl. The median age at diagnosis was 147 months (121-173 months). Clinical manifestations were found in five cases. They were all unicentric Castleman disease (6 abdominal mass, one left infraclavicular mass). All patients were operated with postoperative period uneventful. The median time of postoperative follow up was 22.7 months (11-53 months) with no signs of relapse.*

Conclusions: *Pediatric Castleman disease is a rare benign lymph node hyperplasia, it can be localised or disseminated. Operation is the treatment of choice for localised Castleman disease.*

Key words: *Castleman disease, angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, lymph node hamartoma.*

I. INTRODUCTION

Castleman disease is a rare disorder of lymph node proliferation, first described by Benjamin Castleman in 1956, characterized by an increase in the size of focal or diffuse lymph nodes. The disease is usually divided into 2 types, hypervascular and plasmacytic patterns based on microscopic pathology. The disease is also divided into localized or diffuse based on general lesions [1-7]. Clinical manifestations of Castleman disease vary widely from asymptomatic to nonspecific features such as fatigue, weight loss, anemia and high fever [1,2,3,4,5]. Therefore, diagnosis and treatment are often difficult.

This condition is mainly observed in adults with lesions in the chest accounting for about 70% and only about 10% in the abdominal cavity [4]. This is a rare disease in children, especially in the abdominal cavity.

II. MATERIALS AND METHODS

We conducted a retrospective review of cases of Castleman disease being treated at Children's Hospital 1 from January 2016 to December 2019.

III. RESULTS

There were 7 cases including 3 boys and 4 girls, with the median age at diagnosis of 147 months (121-173 months). Five patients were hospitalized for clinical manifestations of fatigue, loss of appetite, weight loss, pallor, and fever. For case 3, the

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patient had high fever (39ºC) without identified site of infection except very high CRP, leukocyte 17.3 k/ul with neutrophil accounted for 71% and was treated by intravenous broad-spectrum antibiotics. In the following days the patient continued to have intermittent fever with CRP almost unchanged.

Table 1: Clinical characteristics and laboratory profile

ID	Patient	Sex	Age (month)	Clinical signs and symptoms	CRP (mg/dl)	Size of lesion (cm)	Location of lesion	Pathology
1	YVN	Male	139	Asymptomatic		5.2	Retroperitoneal tumor next to pancreas-tic head	Castleman disease with angiofolli-cular lymph node hyper-plasia
2	TNTA	Female	142	Post-peritoneal tumor increased in size (detected at 4 years of age)		6.5	Retroperitoneal tumor next to pancreas-tic head	Castleman disease with angio-follicular lymph node hyper-plasia
3	LTHA	Female	170	Fatigue, pallor, weight loss. High fever for 2 weeks before surgery. Delayed puberty	190	7	Postperitoneal tumor next to pancreas body	Castleman disease with angio-follicular lymph node hyper-plasia
4	TTD	Male	121	Fatigue, anorexia, weight loss, abdominal pain		6.2	Root of jejunal mesentery	Castleman disease with angio-follicular lymph node hyper-plasia
5	NTQ	Female	173	Abdominal pain, fatigue, anemia		7.8	Root of the small bowel mesen-tery	Castleman disease with angio-follicular lymph node hyper-plasia
6	NTL	Male	143	Anorexia, exhaustio/ thalasse-mia	151	3.4	Left supra-clavicular region	Castleman disease with angio-follicular lymph node hyper-plasia
7	NTUN	Female	145	Abdominal pain	178	4.4	Root of the small bowel mesen-tery	Castleman disease with angio-follicular lymph node hyper-plasia

One patient had been diagnosed with an intra-abdominal tumor at the age of 4 without any treatment because it was suspected of an adenoma of the pancreatic head and showed no clinical manifestations other than a slow increase in size. One patient was diagnosed when being treated as digestive disorder.

They were all unicentric Castleman disease including 6 cases with abdominal mass, one case with left supraclavicular mass). The median diameter of the lesion was 5.79 cm (3.4 - 7.8 cm).

All of these cases were localized Castleman disease with pathological results of Castleman disease with angiofollicular lymph node hyperplasia.

Table 2: Treatment and follow up

ID	Patient	Preoperative diagnosis	Method of surgery	Early postoperative period	Duration of follow up (months)	Outcome
1	YVN	Pancreatic tumor	Resection of tumor/ open surgery	No complication	43	No evidence of relapse
2	TNTA	Pancreatic tumor	Resection of tumor/ laparos-copic surgery	No complication	28	No evidence of relapse
3	LTHA	Tumor next to the head of pancreas	Resection of tumor/ open surgery	No more fever, normalization of CRP, no complication	22	No evidence of relapse
4	TTD	Mesenteric tumor suspected of lymphoma	Resection of tumor/ laparos-copic surgery	No more abdominal pain and fatigue, gain of appetite, no complication	22	No evidence of relapse
5	NTQ	Mesenteric tumor suspected of Castleman disease	Resection of tumor/ open surgery	No more abdominal pain and fatigue, gain of appetite, no more anemia, no complication	23	No evidence of relapse
6	NTL	Tumor at the supraclavicular region suspected of Castleman disease	Resection of tumor	No more fatigue, gain of appetite, normalization of CRP, no complication	18	No evidence of relapse
7	NTUN	Mesenteric tumor suspected of Castleman disease	Resection of tumor/ open surgery	No more abdominal pain, gain of appetite, , normalization of CRP, no complication	11	No evidence of relapse

At the beginning, Castleman disease was not thought of in the first four patients. Patient 6 had a needle biopsy before complete resection but the diagnosis was not confirmed. The remaining cases were not performed needle biopsy due to the location of the tumor as well as the characteristics of vascular proliferation found on computed tomography.

The lesions were completely resected in all 7 cases with both open and laparoscopic surgery depending on the location and sizes of the tumors.

All patients recovered well, clinical symptoms

quickly disappeared right in the first few days after surgery. Antibiotics for cases with fever were discontinued as soon as the results of pathological findings were obtained and CRP levels decreased to 33 mg/dl on the third postoperative day.

These patients were discharged and monitored based on clinical manifestations and periodic ultrasound examination with a median follow-up time of 22.7 months (11-53 months). Results at follow-up showed a physical recovery, gain of appetite as well as the disappearance of symptoms and no signs of relapse.

IV. DISCUSSION

Castleman disease is a benign proliferation of lymphocytes and cytoplasm, also known by other names: giant lymph node hyperplasia, lymph node hamartoma, angiofollicular lymph node hyperplasia [4].

Since the first case with lesions locating in the anterior mediastinum in adults was described by Castleman et al in 1954, an increasing number of cases have been reported with various locations of the lymphatic system. Castleman disease appears to occur in any location of the body's lymphatic system, with the most common site being the anterior mediastinum accounting for about 70%, only less than 10% in the abdominal cavity followed by the neck [2,4].

Six out of 7 cases in our report had intra-abdominal lesions, perhaps a coincidence to help us learn from the diagnosis and treatment of this rare disease. However, we believe that many cases of Castleman disease in the mediastinum as well as many other sites have not been detected due to the absence of clinical manifestations such as the case of patient 2 showing that this disease can progress silently asymptomatic for years.

Although the pathogenesis is still poorly understood, several reports have noted an association between clinical manifestations and an increase in Interleukin 6 [2]. Clinically, the multicentric Castleman disease with mainly cytoplasmic pattern in microscopic examination often presents with systemic symptoms such as enlargement of lymph nodes, fever, fatigue, weight loss, autoimmune disorders, recurrent infections, anemia, hypoalbuminemia, increased CRP, etc [4,6,7].

Five out of seven cases in our report showed symptoms despite the pathological results being angiofollicular lymph node hyperplasia. Previous reports have not shown an association of tumor size with clinical symptoms.

In order to diagnose Castleman disease, diagnostic imaging tests such as ultrasound or chest and abdomen CT scans are recommended for patients with symptoms such as fatigue, loss of appetite, anemia, prolonged fever but not yet found the cause. Screening ultrasound during routine physical exams is recommended to detect lesions without clinical manifestations.

Until now, surgical removal of the entire lesion is the first-choice method for the treatment of unicentric Castleman disease. The disease is treated right after diagnosis, although no studies have shown the ability and time for the unicentric disease to turn into multicentric disease, but the risk of progression to malignancy (lymphoma) has been reported [1,3,5].

The proliferation of blood vessels of the lesion [7] makes needle biopsy dangerous. On the other hand, the biopsy results obtained are also very difficult for definitive diagnosis. Therefore, surgical removal of the entire lesion is usually performed without prior pathological diagnosis.

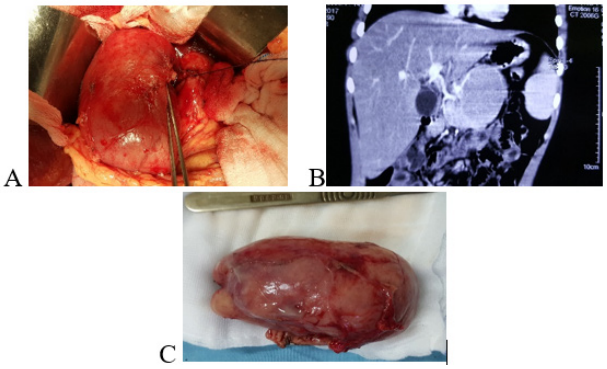
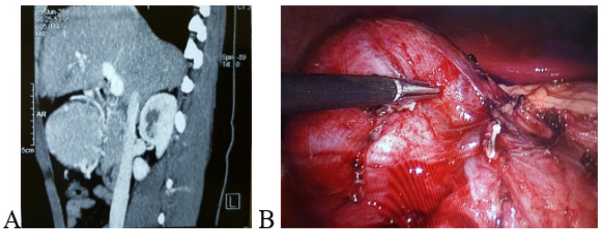


Figure 1: Open surgery to treat Castleman disease (A,B: Lesions on CT scan and during surgery; C: Lesion from complete resection of the tumor) (Patient LTHA).

All 7 of our cases were indicated for total surgical resection based on computed tomography evaluation. During the operation we noted that the surgery was relatively uneventful due to the relatively clear limitation of the lesion, but care must be taken to reveal and protect important blood vessels, which in our cases are visceral artery, mesenteric artery and carotid bundle. Lesions may be in one location but may include multiple lymph nodes and need to remove all of them.

It seems that lesions may be removed either by open or laparoscopic surgery, even though lesions locating adjacent to important blood vessels can make laparoscopic surgery more dangerous. Laparoscopic surgery is also helpful for us to locate the lesion and select the appropriate abdominal route in operation. Preoperative embolization by intravascular intervention - in cases of extensive vascular hyperplasia and in lesions at unfavorable locations – to help a complete resection has been reported [7].

Figure 2: Laparoscopic surgery in the treatment of



Castleman disease
(Patient TNTA).

The patients recovered well and there were no complications. We noted a rapid disappearance of symptoms in two cases ID 3 and 4 right in the first few days of postoperation, especially the CRP level of the third case decreased to 33 mg/dl on the third postoperative day. It seems that the abrupt elimination of secreting chemicals from the tumors (such as IL6) is the cause of this recovery but we have not found an appropriate answer to the clinical manifestations of the two remaining cases although the pathological results of all 4 cases were Castleman disease with angiofollicular lymph node hyperplasia.

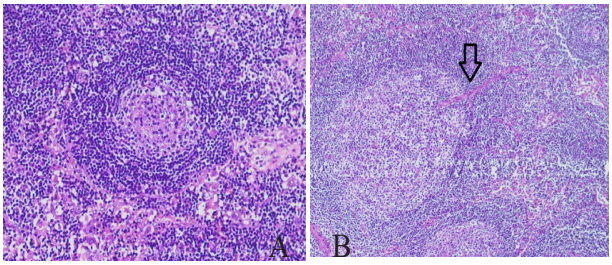


Figure 3: Microscopic images of Castleman disease with angiofollicular lymph node hyperplasia
A. Hyperplasia of follicles in the lymph node.
B. "Lollipop" sign (head of arrow)
(Patient LTHA).

Many reports show that for unicentric Castleman disease, surgical removal can be completely cured, but there are cases of relapses after many years [1-7]. Therefore, it is necessary to monitor long-term for cases of surgical removal.

Relapse or unresectable lesions or multicentric disease can be treated with a variety of therapies such as corticosteroid monotherapy or chemotherapy. Other methods currently being applied, such as interferon alpha, retinoic acid and anti-IL6 monoclonal antibodies, also show promising results.

V. CONCLUSIONS

Castleman disease is a rare disease in children with a diverse clinical presentation characterized by proliferation of lymph nodes with single or diffuse lesions. Complete surgical removal is the treatment of choice for unicentric Castleman disease.

Ultrasound and computed tomography are effective means of detecting the disease.

The outcome of surgery is favorable, but patients need long-term follow-up to check for a relapse.

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