TREATMENT OF KAPOSIFORM HEMANGIOENDOTHELIOMA WITH KASABACH-MERRITT SYNDROME BY CORTICOSTEROIDS AND VINCRISTINE

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ABSTRACT

Objectives: *To evaluate the results of corticosteroids and vincristine in the management of Kaposiformhemangioendothelioma(KHE) with Kasabach-Merritt syndrome.*

Materials and Methods: *Case series review.*

Results: *Six cases had KHE with Kasabach-Merritt syndrome and were treated by corticosteroids in combination with vincristine. The complete response, partial response and no apparent response were achieved at 50%, 33.3% and 16.7% among the study group respectively. Vincristine had mild and transient side effects compared to corticosteroids.*

Conclusion: *Corticosteroids and vincristine may be first-line therapy in the management of KHE with Kasabach-Merritt syndrome.*

Key words: *Kaposiformhemangioendothelioma, Kasabach-Merritt syndrome, vincristine*

I. INTRODUCTION

Kaposiformhemangioendothelioma (KHE) is a rare vascular tumor that usually occurs in infancy and early childhood. Over 70% of KHE cases are associated with Kasabach-Merritt syndrome or phenomenon (KMS or KMP), a life-threatening constellation of thrombocytopenia, coagulopathy and purpura with a mortality of 20%[1]. Thus, enlarging tumors and tumors with KMP often require early interventions. Today, there is no evidence-based standard therapy for the disease. Systemic corticosteroid has been used as a first-line therapy for the treatment of KHE, despite the relatively low response rate and high recurrence rate. Vincristine (VCR), an inhibitor of endothelial proliferation, is a promising approach for treating KHE, especially for steroid-resistant KHE. Other treatment modalities are interferon, radiotherapy, embolization, anti-platelet agents (aspirin), propranololand sirolimus, which have been used alone or in combination are reserved as second- or third-line therapies[2]. Nevertheless, none of the treatments mentioned above has been reported to have a uniform and reproducible effect. Therefore, we conducted a study to describe and evaluate the effects of the treatment of KHE associated with KMS by systemic corticosteroids and VCR.

II. MATERIALS AND METHODS

2.1. Patients

Patients were diagnosed with KHE by the presence of a large vascular tumor which had typical imaginary results on Doppler color ultrasound and CT scan; and with KMS characterized by severe

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thrombocytopenia (<30000/mm^3). Coagulation tests were also performed to identify hypofibrinogenemia and elevated D-dimers levels in KMS. The histological biopsy was not mandatory except when the clinical manifestations were not typical of KHE.

2.2. Method

This was a case series review to evaluate the effect of therapy in KHE associated ith KMS from January 2013 to December 2015. With follow-up >6 months at least, the diseases were classified into three groups, as follows:

- Complete response (normal platelet count and coagulation profile, mass reduction>80%);

-Partialresponse(plateletcount=40.000–100.000/mm^3, coagulation profile normal or abnormal, mass reduction >50%);

-. No response (platelet count <40.000/mm^3, coagulation profile abnormal, and mass reduction <50% or increasing).

Data analysis were conducted by SPSS 18.0. Continuous variables were presented by median (interquartile range) and categorical variables were presented by frequency (percentage).

III. RESULTS

Six patients with KHE and KMS were enrolled into the study. The characteristics of patients were presented in Table 1. The proportion of male:female was 1:1. The median age of patients were 3 months old (range: 1-16 months old). The median follow-up period was 15 months (range: 7-26 months). All patients had large KHE with the diameter of more than 10cm. Patients received previously attempted treatment by corticosteroids in 33.3% (2/6 cases), the remaining had not been treated by any modalities. All patients had one single hemangioendotheliomainvading to adjacent regions, developing on the lumbar region (n=2 [33.3%]), extremities (n=2 [33.3%]), face 16.7% and retroperitoneum (n=1 [16.7%]).

Patients' common features at diagnosis were anemia, purpura, gastrointestinal bleeding in one case; acute respiratory distress due to compression from the large hemangioendothelioma complicated by anemia and/or severe bleeding in two cases. One patient had infection and ulceration at the hemangioendothelioma resulting in hamorrhage of the tumor.

All patients had severe thrombocytopenia at diagnosis with the median of platelet count of 10.500/mm^3 (range: 4.000-17.000/mm^3). Coagulopathy and hypofibrinogenemia occurred in all patients with the median fibrinogen levels of 0.8 g/l (range: 0.6-0.9 g/l).

High dose of corticosteroids at 4-10mg/kg/day during the severe stage were given immediately to all patients and then prednisone was tapered at every 2-week interval when the clinical conditions were stable (ie., no new hemorrhagic lesions, elevation of platelet count, no further increase in size of the tumor). The mean duration of corticosteroid therapy was 23±6 weeks. Vincristine was given intravenously at 0.05 mg/kg per dose weekly for four times, followed by monthly for six times. Only one out of 6 patients with partial response had to use VCR for 9 months.

The rates of complete, partial and no response were 50% (3/6 cases), 33.3% (2/6 cases) and 16.7% (1/6 cases) respectively. The platelet counts normalized after an average of 3.6 ±1.2 weeks, then tended to decrease but remained above 50.000-100.000/mm^{3}during the maintenance by corticosteroids and VCR. Fibrinogen levels and consumptive coagulopathy returned to normal after an average of 3.3±0.8 weeks. Reduction in size of the tumor by 50% was achieved after 4.2±0.5 weeks, and by 80% after 27.2±8.9 weeks. The recurrence rate of KMS was 33.3% (2/6 cases). Treatment-related side effects were presented in Table 2 with one case of transient increase in hepatic enzymes after the usage of VCR.

Table 1. Characteristics of KHE with Kasabach-Merritt syndrome

	Age at diagnosis (months)	Sex	Location	Estimated size of tumor (cm)	Previously attempted treatment	Manifestations at diagnosis	Platelet count at diagnosis ($x10^3/mm^3$)	Fibrinogen levels at diagnosis (g/l)	Follow-up (months)	Outcome
Pt 1	4	male	Lumbar and sacrococcygeal region	22x15	none	Gastrointestinal bleeding, anemia, acute respiratory distress	8	0.6	14	Complete response
Pt 2	2	male	Right lumbar and retroperitoneum	16x13	none	Anemia, purpura	17	0.9	7	No response
Pt 3	16	male	Right thigh and groin, scrotum	13x14	none	Ulceration with bleeding at the tumor, anemia, purpura	12	0.8	9	Complete response
Pt 4	1	female	Lumbar and sacrococcygeal region, left anterior abdominal wall	24x17	none	Anemia, purpura, ecchymosis, gastrointestinal bleeding	4	0.7	15	Partial response
Pt 5	7	female	Arm, shoulder and right chest	18x112	Steroid	Purpura	15	0.7	15	Partial response
Pt 6	1	female	Face, chin and left shoulder	12x9	Steroid	Anemia, acute respiratory distress, purpura and ecchymosis	9	0.9	26	Complete response

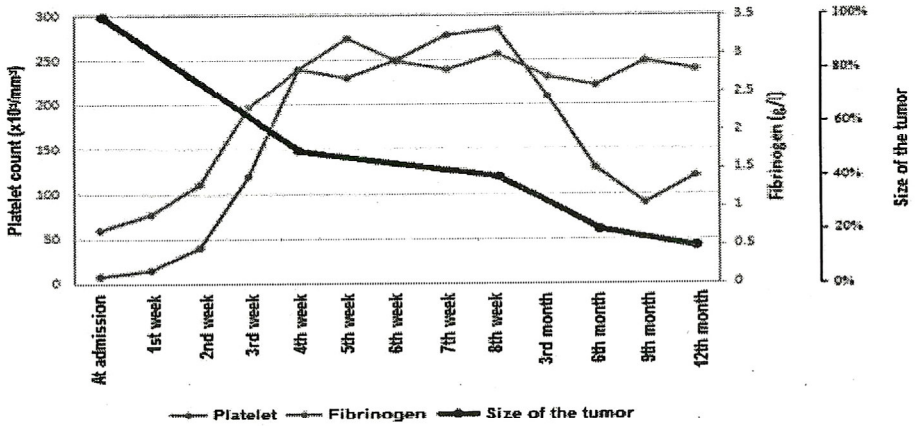

Figure 1: Changes in size of the tumors, platelet count and fibrinogen levels after treatment

Table 2. Treatment-related side effects

Side effects	n (%)
Vincristine	
Constipation	1 (16.7)
Elevation of transaminases	1 (16.7)
Corticosteroids	
Retardation	3 (50)
Cushing's syndrome	2 (33.3)
Opportunistic infection	1 (16.7)

IV. DISCUSSION

KHE is not a malignant disease but is characterized by local invasion that can cause serious complications such as Kasabach-Merritt syndrome with severe thrombocytopenia and coagulopathy. Most cases had KHE that are giant in size and the tumors may be located in dangerous locations such as head and neck area causing compression, or lie deep within the thoracic cavity and retroperitoneum making surgicalintervention almost impossible.

To date definite treatment guidelines for KHE with KMS are not available. The principle of treatment is to make the tumors reduce in size or surgical tumors removal to restore the platelet count and coagulation factors. Traditionally, systemic corticosteroids have been recommended as first-line treatment for KHE with KMS in situations where surgical excision is not possible. However, one-third of cases may not respond to treatment or recur with corticosteroids as monotherapy.

Haisley-Roister and colleagues reported all 15 patients with KHE complicated by KMS had an increase in platelet count of at least 20.000/mm^3 after 4 weeks of treatment, and platelet counts passed 150.000/mm^3 at an average of 5.3 weeks [3]. Thirteen patients had a decrease in the size of their tumor over an average of 22 weeks. All 13 of the patients with abnormal fibrinogen levels showed an increase in fibrinogen weeks of at least 0.5 g/L over an average of 3.4 weeks. The recurrence rate in the author's study was 26.7% (4/15 cases). One case was reported to have side effects on the peripheral neuropathy related to VCR. Our study also showed the mean time for normalization of platelet count was 3.6 ±1.2 weeks while fibrinogen levels and consumptive coagulopathy returned to normal after an average of 3.3±0.8 weeks. Regarding treatment-related side effects, of the 6 patients in our study only 1 case had constipation and 1 case had transient elevated liver enzymes that were associated with the usage of VCR. The recurrence rate with medical therapy alone in our study was 33.3% which is similar to other authors. Nguyen QuangAnh treated 10 patients with KMS by corticosteroids for 1 to 6 months followed by complete surgical removal of the tumors without reported recurrence; however, all of these cases were accompanied by a resectable site of the tumors [4].

According to the literature, the duration of treatment with corticosteroids in KHE with KMS is from several weeks to more than 1 year. In our study, the averagetime of corticosteroid therapy was 23±6 weeks. In Drucker AM and Wang Z's reports, the time of treatment with vincristine was 7 months and additional doses were added if necessary, and this approach is similar to our study [2, 5].

A recent study based on expert opinion regarding the first choice in medical treatment for KHE with KMS found that 50% chosecorticosteroids combined with vincristine; others chosemonotherapy with corticosteroids in 29%, vincristine in 8%, cyclophosphamide in 4%, rapamycinein 4%, and the remaining chosecorticosteroids combined with propranolol in 8%[6]. More and more studies on the use of VCR as a monotherapy or combination therapy for KHE with KMS because it is effective in reducing size of the tumors, restoring platelet count and clotting factors and having fewer side effects compared to corticosteroids [5, 7-9].

V. CONCLUSION

KHE with KMS is a rare benign condition but difficult in management because the lesion is often very large and located at invasive regions complicated by consumptive coagulopathy and thrombocytopenia. Initial medical treatment with

corticosteroids combined with vincristine is one of the options for severe cases which are impossible for surgical intervention. Further large study with long-term follow-up as well as multifaceted management are needed to evaluate the outcome of KHE with KMS.

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