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ORIGINAL ARTICLE

COMPARISON OF BENIGN AND MALIGNANT MEDIASTINAL MASSES IN CHILDREN-CLINICAL FEATURES, ETIOLOGY AND TREATMENT OUTCOME: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Introduction: Mediastinal masses in children pose a diagnostic as well as therapeutic dilemma to clinicians. There is paucity of information in existing literature regarding relative prevalence of various etiologies and their management outcomes in children.

Methods: In this single institution observational prospective studycarried out between August 2013 and July 2017, 86 children with mediastinal masses were evaluated for the etiology, clinical features and treatment outcomes. Prevalence of superior mediastinal syndrome (SMS), factors associated with its occurrence and its clinical implications were also determined.

Results: Out of 86 children with mediastinal masses, 28 (32%) had benign masses and 58 (68%) had malignant masses. Tuberculosis (TB) was the commonest among benign mediastinal mass seen in 22 (79%) children. Among the common malignant masses, Hodgkin's lymphoma was seen in 16 (27%), T cell acute lymphoblastic leukemiawas seen in 14 (24%) and neurogenic tumors were seen in 8 (13%) children. SMS was present in 40 (45%) children. SMS was present in 8 (24%) patients with T cell acute leukemia (p=0.01). Solid tumors in advanced stage i.e. stage III and IV were more likely to have SMS (odds ratio 2.7, p=0.29). The overall progression free survival was 76% and 97% for malignant and benign mediastinal masses respectively at the end of median follow up period of 24 months (p=0.01). The subgroup with superior mediastinal syndrome had relatively acute presentation and poor final outcome.

Conclusion: In children, malignant mediastinal masses are more common than benign mediastinal masses and they have relatively poor prognosis. Hodgkin's lymphoma and TB are the most common cause of malignant and benign mediastinal masses in children respectively. T cell leukemia is the most common cause of SMS. The prognosis was comparatively dismal for the subgroup with SMS.

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Introduction

Mediastinal masses have always been a diagnostic as well as therapeutic dilemma for medical professionals. Most of the clinical studies on mediastinal masses are retrospective single institutional studies mainly based on case records.[1,2] Moreover the study population in these studies included children and adults as well as benign and malignant mediastinal masses both, without any accurate comparison between the clinical presentation and management outcome of benign and malignant mediastinal masses.[2] The clinical profile of benign and malignant mediastinal masses in children is different when compared to adults.[3] Most of these studies were performed in other parts of the world and may not be reflective of Indian patient cohort.[4] Information on prevalence of superior mediastinal syndrome (SMS) and factors associated with its occurrence is scarce in literature. The current study was planned to determine the prevalence and profile of malignant tumors presenting as mediastinal masses in children. The outcome of these tumors following chemotherapy and determinants of SMS were also evaluated. At the same time all the children presenting with benign mediastinal masses were also evaluated for their clinical profile and management outcome and the same was compared with malignant mediastinal masses.

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Methods & Materials

The study was conducted after obtaining clearance from Institute Ethics Committee. On the basis of previous clinical study conducted by Mohammad et al[2], the minimum sample size was estimated to be 70, with power of 90% and alpha error of 5%. The authors

prospectively evaluated 86 children aged 0-12 years with benign and malignant mediastinal masses with significant mediastinal widening on chest x-ray and/or CT scan (with/without SMS) from August 2013 through July 2017 for their clinical presentation, etiology and treatment outcomes. Children with symptom duration of <4 weeks were considered to have acute presentation. Children presenting with stridor, respiratory distress, facial or conjunctival congestion with engorged veins along with mediastinal mass in chest X ray and/or CT scan were considered to have SMS. If history, physical examination and chest X ray and CT scan showed features more favoring benign mediastinal masses, than tuberculosis (pulmonary and extrapulmonary) were ruled out as this is supposed to be currently the most prevalent cause of benign mediastinal masses in low and middle income countries.[5]

Benign mediastinal masses

Children with history of chronic cough, evidence of tuberculosis (TB) in pulmonary parenchyma or elsewhere in body, mantoux positivity, active contact with a TB patient in family or community and subacute/ chronic course without other features of malignancy were considered clinically to have benign mediastinal masses for the purpose of study. On the other hand, children with altered hematological parameters, with severe anemia or thrombocytopenia, severe bony pain, acute/subacute course with hepatosplenomegaly were considered clinically to have malignant mediastinal mass. For differentiating between the both help of radiology, pulmonology and pediatric oncology experts' help were also taken. Apart from the routine diagnostic tests for TB like complete blood count with erythrocyte sedimentation rate (ESR), mantoux test, family survey with chest X ray to trace possible tubercular contacts, gastric aspirate/sputum for acid fast bacilli (AFB), GeneXpert and MGIT(Mycobacterium Growth Indicator Tube) culture were also done in children with suspected benign mediastinal masses.[6] For children requiring lymphnode biopsy for confirmation, it was planned from most easily accessible location, either true-cut or excision biopsy, done by direct open biopsy, USG/CT or video endoscopy assisted (for mediastinal lymphnodes). Patients were diagnosed as TB based on clinical or bacteriological confirmation by either GeneXpert or microscopy and culture.[7] Disseminated TB was defined as presence of TB at 2 different sites. Treatment naïve patients were started on category 1 antituberculous therapy (ATT) with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months in intensive phase, followed by continuation phase with two drugs (isoniazid and rifampicin) for 4 months. Children with default or treatment failure cases previously were started on category 2 ATT with addition of streptomycin to the 4 drugs in intensive phase and total duration of ATT was increased to 9 months. Multi-drug resistant tuberculosis (MDR-TB) if the tubercular bacilli was resistant to rifampicin and isoniazid on MGIT culture.[8] For children with suspected benign thymic hyperplasia, classic radiologic features like lobulated thymic contour, Sail sign in chest X ray, clinical profile and age of the child were taken into account to establish the final diagnosis.[9] Sarcoidosis was diagnosed on the basis of increased serum angiotensin converting enzyme (ACE) level, increased urinary calcium–creatinine level, non-caseating granuloma or altered CD4/CD8 ratio in lymph node biopsy or bronchoalveolar lavage fluid.[10] Bacterial or fungal infections were diagnosed by culture or serological tests. Clinical features, factors associated with SMS, treatment received (category and duration of ATT, intravenous or oral antibiotics, corticosteroid) and final treatment outcome were determined.

Malignant mediastinal masses

Complete blood counts and peripheral smear alone or along with bone marrow examination was done for all patients. If this showed blast cells, a diagnosis of an acute hematological malignancy was made which was further characterized by flow cytometry of blood/ bone marrow examination.[11] In other children, CT scan of the neck, chest or abdomen was done especially for solid tumors. Tissue diagnosis for the malignancy was established by the least invasive procedure (FNAC or biopsy of mediastinal mass, other lymph node/ tumor mass).[12] Treatment outcome was determined in the form of remission, relapse or mortality as per standard guidelines.

SMS syndrome

Children with benign and malignant mediastinal masses were evaluated for evidence of SMS.[13] The factors associated with this syndrome were evaluated e.g. age and sex distribution, histopathological diagnosis, site and stage of tumor, duration of symptoms before presentation to health care system.

Statistical analysis

Data were collected on predesigned proforma, managed using MS Excel spreadsheet and analyzed using Stata software. Frequency (percentage and its 95% confidence interval) was computed for each tissue diagnosis, clinical feature and treatment outcome of mediastinal malignancy. For determining association of different factors with SMS, chi square test was used and odds ratio with 95% confidence interval were used. P value <0.05 was considered significant.

Results

Out of 86 children, 28 (32%) had benign mediastinal masses and 58 (68%) had malignant mediastinal masses. Clinical characteristics of benign and malignant mediastinal masses are given in table 1.

Among the children with benign mediastinal masses, male: female ratio was 16:12. Mean age of clinical presentation was 8.3±3.1 years. Twenty-two (79%) children had TB, of which 15 were bacteriologically confirmed and 10 had disseminated TB. Seventeen children responded to category 1 and 5 children required category 2 ATT. None of the children had MDR-TB. Only 1 child with disseminated TB did not respond to treatment and died following respiratory failure. Five children (mean age of presentation 3.2 years) had benign thymic hyperplasia and 4 were asymptomatic and this was mainly an incidentally detected finding on chest X-ray, only one child had recurrent wheeze. One child had sarcoidosis who responded to oral corticosteroids. Seven children (25%) had evidence of SMS, out of which 6 were boys and 5 had disseminated

TB (p= 0.04 and 0.02 respectively). Remaining children (97%) were completely cured and asymptomatic at median follow up of 22 months.

Among the children with malignant mediastinal masses, male: female ratio was 45:13. Mean age of presentation was 6.6±3.4 years. The etiologies of malignant mediastinal mass are given in table 2. Thirty-three (57%) children had SMS (Table 2). Regarding etiology only T cell acute leukemia had very strong association with SMS (p=0.01). Solid tumors in advanced stage i.e. stage III and IV were more likely to have SMS (odds ratio 2.7, p=0.29). Children with SMS had a more acute presentation as compared to those without the same (p=0.03). Overall 40 (76%) children with malignant mediastinal mass had favorable outcome at mean duration of follow up of 24 months, as compared to 97% in children with benign mediastinal masses (p=0.01). In the study group, Hodgkin's lymphoma and B cell leukemia had better prognosis with 87% and 66% favorable response respectively. T cell leukemia and metastatic neuroblastoma had worse prognosis with only 50% of these children having favorable outcome in both cases. The sub-group with SMS had relatively poor prognosis with survival rate of 67% while those without SMS had survival rate of 83% (p=0.05, odds ratio 4.6). Prevalence of SMS was also statistically more in children with malignancy as compared to benign lesions (57% vs 25%, p=0.01).

Age wise break up of different etiologies of mediastinal mass is given in Table 2. Age of presentation, gender of the child and anatomical site of mediastinal mass was found to have no correlation in predicting SMS in both benign and malignant mediastinal masses (Table 3). Out of 24 children with acute presentation of symptoms, 20 (83.3%) children had SMS. On the other hand, out of the 62 children with subacute/chronic presentation, only 16 (25.8%) children had SMS (p=0.01).

Discussion

Fever and cough were the most common symptoms of benign mediastinal masses in our study and TB was the most common cause. Similar clinical finding had been demonstrated previously by Temeset al.[14] Fever, respiratory distress and cough were the most common presentation of mediastinal malignancy in our study apart from non-specific constitutional symptoms. Previously Shrivastav et al and Aroor et al also showed similar findings in their studies.[1,15] In our study 56% of children with malignant mediastinal masses had superior mediastinal syndrome, which is significantly higher than other studies. It could be due to the fact that these studies were comprised of heterogeneous population including both benign and malignant mediastinal masses. Similar results were also demonstrated in clinical studies performed by Adegboye et al and Arya et al.[16,17]

In our study, malignant mediastinal masses were more common than benign mediastinal masses. Temes et al in their study also showed malignant mediastinal masses are more common than benign mediastinal masses in children unlike adults.[14] However, the predominance of malignant mediastinal masses in a setting with high prevalence of tuberculosis can be explained by referral bias, as the study was carried out at a tertiary center and malignant masses are more likely to be referred for evaluation. Similar results had been previously shown by Simpson et al in their clinical review.[18]

The most common etiology of malignant mediastinal mass in our clinical study was Hodgkin's lymphoma followed by T cell acute leukemia, Non Hodgkin lymphoma and neurogenic tumor. Temes et al in their study showed Hodgkin's lymphoma to be the most common mediastinal mass in children.[14] Studies based on adults like Shrivastav et al on the other hand showed thymoma to be most common mediastinal malignancy.[1]

Table 1. Clinical features in children with benign and malignantmediastinal masses

Clinical features	Benign masses (N=28)	Malignant masses (N=58)
Fever	21 (77%)	49 (84%)
Lymphadenopathy	20 (74%)	48 (82%)
Pallor	6 (21%)	39 (67%)
Respiratory distress	7 (25%)	30 (51%)
Cough	20 (74%)	25 (44%)
Pleural effusion	8 (29%)	18 (31%)
Facial puffiness	6 (21%)	13 (22%)
Stridor	4 (14%)	11 (19%)
Pericardial effusion	1 (3%)	7 (12%)
Seizure	–	6 (9%)
Bony pain	–	4 (7%)
Chest pain	1 (3%)	4 (7%)
Dysphagia	–	1 (1.5%)
Change in Voice	–	1 (1.5%)

Table 2. Etiology of mediastinal masses and age wise distribution in children and prevalence of Superior Mediastinal Syndrome (SMS)

Etiology	No of children	SMS	Age (Mean ± SD in years)
Benign masses			
Tuberculosis	22	7(32%)	6.4±2.6
Benign thymic hyperplasia	5	0	3.4±1.2
Sarcoidosis	1	0	8.5
Malignant masses			
Hodgkin Lymphoma	16	7 (44%)	8.3±2.9
T cell acute lymphoblastic leukemia	14	13 (93%)	10.1±1.3
B cell Acute lymphoblastic leukemia	9	0	6.3±2.4
Neuroblastoma	8	6 (75%)	3.2±1.1
Non Hodgkin Lymphoma	5	4 (80%)	5.3±1.8
Acute myeloid leukemia	2	0	7.8±1.1
Malignant peripheral nerve sheath tumor	2	2 (100%)	8.1±1.2
Rhabdomyosarcoma	1	1 (100%)	11.5
Metastatic Nasopharyngeal carcinoma	1	0	10.5
Total	86	40(45%)	6.8±2.1

Table 3. Factors associated with SMS

	Benign Tumors (n=28)			Malignant Tumors (n=58)		
	SMS (n=7)	No SMS (n=21)	p value	SMS (n=33)	No SMS (n=25)	p value
Age (in years)	6.48±2.74	6.79±2.31	0.77	7.25±3.64	5.92±3.23	0.37
Male	5 (71.4%)	17 (81%)	0.47	26 (78.8%)	19 (76%)	0.52
Female	2 (28.6%)	4 (19%)		7 (21.2%)	6 (24%)	
Anterior mediastinal tumors	6 (85.7%)	20 (95.3%)	0.44	27 (81.8%)	23 (92%)	0.23
Posterior mediastinal tumors	1 (14.3%)	1 (4.7%)		6 (18.2%)	2 (8%)	

T cell leukemia was the most common mediastinal mass presenting with the SMS in our study. Neurogenic tumor and Hodgkin's lymphoma constituted a significant proportion among the rest. Arya et al in their retrospective study also found out T cell leukemia to be the most common cause of superior mediastinal syndrome in children.[15]

Previously Fraga et al showed a survival rate of 70% and Temes et al showed a survival rate of 74% among the children with mediastinal malignancy in their studies.[4,14] In our study group, survival rate was 76%, which is comparable to previous studies. In the children with SMS a survival rate of 52% and 56% were found out in the studies performed by Arya et al and Takeda et al.[17,19] In our study the corresponding survival rate was 67%. Hence, it can be safely concluded that with timely adequate chemotherapy, a good prognosis can be expected in most of the children with mediastinal malignancy, also shown in the clinical study performed by Gunn et al.[20] On the contrary, the prognosis was relatively dismal for the subgroup with SMS.

Tuberculosis was the most common cause of benign mediastinal mass in children and most children responded favorably to antitubercular therapy. This result was consistent with previous literature described by Fraga et al.[4] The outcome of benign mediastinal masses were better as compared to malignant counterpart in our study and similar results were also found by Grossfield et al in their clinical study.[12]

Conclusion

Tuberculosis is most common cause of benign mediastinal masses and Hodgkin's lymphoma and T cell leukemia are most common causes of malignant mediastinal masses. T cell leukemia is the most common cause of the SMS. Malignant mediastinal masses are at more risk of developing SMS. Advanced stage of solid tumors predisposes for SMS. Presence of the superior mediastinal syndrome is a poor prognostic factor.

Compliance with Ethical Standards

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Conflict of Interest: None

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