Critical Care Needs and Outcome of Pediatric T cell Lymphoblastic Leukemia or Lymphoma with Superior Venacaval Syndrome

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Abstract

Background- Superior Vena Cava Syndrome (SVCS) is a life-threatening oncological emergency affecting children with T-cell Acute lymphoblastic Leukemia (T-ALL)/ T-Lymphoblastic Lymphoma (T-LBL). This can prove fatal if not managed appropriately and promptly. **Method-** We describe critical care needs and outcome of T-ALL/T-LBL patients managed in our unit from 1 st May 2016 to 31 st March 2021. **Result-** Twenty-three of the 120 pediatric ALL/LBL patients (19%) managed in our unit had T-ALL/T-LBL. Eleven (48%) patients presented with SVCS. All presented with cough and dyspnea. Chest X-Ray showed mediastinal widening in all patients. Flow cytometry in various body fluids could reach prompt diagnosis in 90% patients and mass biopsy was performed in only 1 patient. Eight patients required Pediatric Intensive Care Unit support. All 11 patients were started on corticosteroids soon after diagnosis of SVCS. The median time to symptom relief was 4 days and that for significant improvement on X-ray was 7days. At a median follow up of 23-months (6-63 months) overall survival and event-free survival was 75%. **Conclusion-** T-ALL/T-LBL patients with SVCS with good critical care can have improved outcomes. Prompt therapeutic interventions like pericardiocentesis can be life-saving. Flow cytometry can be a handy tool for quick diagnosis and help avoid invasive procedures in sick patients.

Introduction

Superior Vena Cava Syndrome (SVCS) refers to signs and symptoms resulting from compression, obstruction or thrombosis of the superior vena cava. The term Superior Mediastinal Syndrome (SMS) is used when tracheal compression also occurs, but the terms are interchangeably used due to coexistence of the two entities. It is known to occur with non-Hodgkin lymphoma, Hodgkin Lymphoma, and T-cell Acute Lymphoblastic Lymphoma(T-ALL) (1). SVCS is a known oncological emergency and can be life-threatening if there is a delay in the initiation of appropriate management. Symptoms include cough, dyspnea, dysphagia, and swelling or discoloration of the neck, face, and upper extremities. Distension of the superficial veins in the chest wall can cause the development of collateral neck veins (2). SVCS is a clinical diagnosis, although plain radiography, computed tomography (CT) of the chest ,and venography may be used for confirmation (3). There is not much published literature highlighting the clinical course and outcomes of T-ALL/T-cell Lymphoblastic Lymphoma (T-LBL) patients who present with SVCS. We describe here the course, critical care needs, and outcomes of this cohort managed at our center.

Material and Method

Data collection

All T-ALL/T-LBL patients <18years of age who presented in our department with signs and symptoms of SVCS including cough, dyspnea, dysphagia and swelling or discoloration of the neck, face and upper extremity between 1st May 2016 and 31st March 2021 were included. Electronic medical records were used for retrospective analysis of the patients' clinical records. The Picture Archiving and Communication System

(PACS) software was used to retrieve radiological data. Clinical notes and telephonic communication were used to document follow up till 30th November 2021.

Approach to diagnosis

Standardized criteria to define mediastinal widening are lacking. However, it is considered that tumor less than 30% of the transthoracic diameter are less likely to be symptomatic for SVCS(1). Hence in our study we have considered a mediastinal measurement of >1/3rd the transthoracic distance at the level of the aortic knob on a supine anterior-posterior view x-ray film as mediastinal widening. Hyperleukocytosis was considered as a total leucocyte count more than 100 x 10^9 /Liter in a patient with leukemia who had respiratory/ neurological symptoms associated with hypoxia secondary to leukocytosis (4).

Flow cytometry was performed on peripheral blood when circulating blasts were present. In their absence, pleural or pericardial fluid was tested by Flow cytometry. Flow cytometry was done using 10 colors, 3 laser BD FACS Lyric/ BD FACS Suite.

Bone marrow examination was done for all patients once they were stable. Those with marrow involvement of [?] 25% were diagnosed as T-ALL. Bone marrow involvement of <25% or no involvement was diagnosed as T-LBL.

Patient management

All our T-ALL/ T-LBL patients were risk-stratified and treated as per ALL-BFM-95 protocol backbone (5). Patients were started on steroids soon after diagnosis of SVCS.

Outcome assessment

Overall survival (OS) and event-free survival (EFS) were the primary endpoints. OS was defined as the period from date of diagnosis to death due to any cause. EFS was defined as the period from the date of diagnosis to relapse, progression, or death. Complete remission (CR) of primary disease was defined as the absence of mediastinal disease on radiological examination. Bone marrow blasts <5% in those with initial marrow involvement was also needed to define CR. Partial remission (PR) was defined as residual disease on radiological examination and /or bone marrow blasts 5-25%.

Result

A total of 120 pediatric ALL/LBL patients were treated in our Pediatric Hematology Oncology and BMT Unit between 1st May 2016 and 31st March 2021. Chest X-ray was routinely performed in all patients diagnosed with ALL/LBL, however CT chest could be done in only 3 patients. Of these, 23 patients (19%) had T-ALL/T-LBL. Eleven (48%) amongst these T-ALL/T-LBL presented with SVCS. Routine chest X-ray helped us diagnose an additional of 6 patients with radiological evidence of mediastinal mass, but had no clinical symptoms of SVCS. All patients were males aged 4-16 years with a median age of 9 years. Six patients (54%) were diagnosed as T-ALL, while the remaining 5(46%) as T-LBL. Demographic details and clinical presentations of these patients are described in Table 1.

The time from onset of symptoms to diagnosis ranged from 1 to 12 weeks (median 3 weeks). Cough and dyspnea as predominant presenting symptoms were seen in all the patients. Examination findings were suggestive of decreased air entry in 5/11 patients (46%), muffled heart sounds in 4/11(36%), and distended neck veins in 4/11 patients (36%). Rarer findings included sternal bulge, facial nerve palsy, pedal oedema and cardiogenic shock in one patient each. Chest X-ray was the 1st radiological imaging done in all patients. Mediastinal widening was seen in all (100%), and pleural effusion was seen in 5/11 patients (45%). All underwent 2D- echocardiography, and pericardial effusion, and cardiac tamponade was noted in 2(18%) and 4(36%) patients respectively. Two (18%) patients had hyperleukocytosis on hemogram. One patient with facial nerve palsy, had negative malignant cytology on CSF and no evidence of CNS disease on MRI brain hence symptoms were thus attributed to SVCS. Central nervous system (CNS) disease was seen in only 1 patient.

Prompt diagnosis of ALL/LBL could be reached in 10 patients (90%) by Flow cytometry. Among these 10 patients, flow cytometric identification of blasts was made in a peripheral blood sample in 3 patients (27%), pleural fluid in 4(36%), pericardial fluid in 2(18%) patients, and bone marrow aspirate sample in 1 patient (9%). Bone marrow aspiration and biopsy was done under local anesthesia in sitting position. In one patient diagnosis could not be reached by any method so treatment was started empirically. CT guided biopsy of the mediastinal mass was performed 24-hours after starting steroids and stabilization the patient. Bone marrow examination was performed in the remaining patients once they were stable after initiation of steroids. Diagnosis was changed from lymphoma to leukemia in 2 patients. Initially, both were diagnosed as lymphoma due to presence of blasts in pleural fluid but later found to have blasts in bone marrow when tested.

Flow cytometry was performed on peripheral blood when circulating blasts were present. As therapeutic and diagnostic measures when indicated, patients underwent intercostal drain placement with continuous drainage for pleural effusion and pigtail catheter drainage was done for pericardial effusion. In view of difficulty and risk of sedation while performing procedures like bone marrow examination or tru-cut biopsy, such procedures were deferred where possible. Diagnosis was attempted by doing flow cytometry on peripheral blood, pericardial/ pleural fluid. All were started on corticosteroids soon after diagnosis of SVCS was established at 60mg/m^2/day of oral prednisolone or equivalent dose of intravenous methylprednisolone or hydrocortisone infusion.

Eight of eleven patients (72%) required pediatric intensive care unit (PICU) admission ranging from 2 to 13 days (median- 4.5 days). Invasive procedures such as pleurocentesis and Pig-tail catheter pericardiocentesis were done in 4/11(36%) patients each. Oxygen supplementation with nasal prongs was required in 9/11 (81%) patients, and endotracheal intubation was required in 2 (18%) patients. Patients with only radiological evidence of mediastinal mass without SVCS fared better than this cohort in the induction period (need for intensive care support 0% vs 72%).

Initial response to treatment was judged by relief of symptoms. Time to onset of clinical response ranged from 1-13 days, with a median of 4 days. The radiological response was judged by the time to a significant decrease of the original mediastinal widening on Chest X-ray, which ranged from 4-20 days with a median of 7 days.

Two patients had thrombosis of bilateral brachial and subclavian veins with extensive collaterals diagnosed by ultrasound Doppler of upper limbs and were treated with low molecular weight heparin. Other known complications of SVCS such as stroke, pulmonary embolism, and recurrent laryngeal nerve palsy were not seen in any of our patients. None of our patients needed any form of surgical intervention such as stenting or thrombolysis.

All our patients were risk stratified and treated as per BMF-95 back-bone protocol. One patient abandoned treatment immediately after initial stabilization and has been excluded from further analysis. Three patients were stratified as high risk and 7 as medium risk as per BFM-95 stratification. The two patients with extensive venous thrombosis received etoposide in place of the last 2 doses of L-asparaginase, and another 1 was switched to BFM-95 High-Risk block in view of persistent metabolically active residual disease on PET-CT scan. Hematopoietic stem cell transplantation (HSCT) was offered to 2 patients. Both abandoned treatment before reaching HSCT.

In our cohort of 11 patients, 3 abandoned treatment at various times points. The follow-up and outcome of this cohort is depicted in figure 1. Six out of the remaining 8 are alive and in remission at last follow up. One patient died of progressive disease and another one died of treatment related complication. At a median follow up of 23-months (range 6-63 months) overall survival and event-free survival was 75%. However, if include the 3 children who abandoned therapy as events then event free survival drops to just 55%.

DISCUSSION

Oncological diseases account for 80-90% of the reported cases of SVCS. The frequency of mediastinal mass

in T-LBL/T-ALL ranges from 66-90% in adult studies and is more in mature T-ALL phenotypes (6). One study identified that almost 50% of children with mediastinal masses presented in emergency with respiratory distress, dyspnea, cyanosis, and they needed immediate intervention (7). Of our patients, 48% of the T-ALL/T-LBL patients presented with SVCS. The most common reason for this presentation is due to the mechanical obstruction caused by the mediastinal mass. Additionally, pleural and/or pericardial effusions may be present which may be diagnosed clinically or radiologically.

SVCS is an oncological emergency requiring prompt commencement of treatment aimed at rapid tumor debulking with intensive chemotherapy and/or radiation therapy, as indicated or feasible. PICU support includes managing airway and circulation , renal replacement therapy etc. (8).

In our cohort, mediastinal widening on X-ray was noted in all patients. 72% of patients required PICU stay. Supplemental oxygen was required in 82%, and endotracheal intubation was required in 18% of our patients. None of our patients required inotrope support or renal replacement therapy. Morin et al. described the clinical presentation and critical care needs of 50 cancer patients (60% hematological malignancy and 40% solid tumor), median age 37 years(25-29years), presenting with SVCS. Pleural effusion, pulmonary atelectasis and pulmonary embolism were seen in 66%, 32%, and 10% patients respectively. Pericardial effusion on echocardiography was noted in 44% patients. Critical care unit interventions like intubation was required in 30%, inotrope infusion in 14% and renal replacement therapy in 6%. Pleural and pericardial drainage was performed in 26%, and 8% patients, respectively (9). Another study from India analyzed 55 patients of T-LBL patients with mediastinal mass with a median age of 18years, 36/55 presented with SVCS. Pleural effusion was seen in 71%, and pericardial effusion was seen in 52% (10).

These patients at presentation are very sick and need urgent commencement of treatment for onset of relief. Invasive painful procedures like bone marrow test or trucut biopsy to reach a diagnosis that requires anesthesia/sedation may not be desirable and feasible since SVCS may confer a higher risk of airway collapse and difficult intubation and ventilation. Also, delays that happen in the process of doing diagnostic tests may be circumvented when these tests can be done reliably on accessible body fluid samples like peripheral blood/ pleural fluid/ pericardial fluid. In our patients, pleurocentesis and pericardiocentesis were done in 36% patients each as therapeutic measure and the fluid was sent for morphology and Flow cytometry which helped in prompt diagnosis. Flow cytometry could identify blasts on peripheral blood and pericardial/ pleural fluid in 90% of patients.

Flow cytometry has long been known to detect blasts in peripheral blood and bone marrow aspirate; however, its efficacy in the detection of blasts on non-hematic body fluids is less well established. Several published data have shown the indispensable role on Flow cytometry in diagnosis and early initiation of treatment including that by Bhaker et al. who evaluated 15 samples from pediatric patients (6-15 years) with Precursor T-cell Lymphoma, and, Czader et al. who analyzed 115 serous cavity effusions from patients aged 2-80yeras of age(mean age- 56 years) with malignant effusion (11) (12). Cesana et al. on 2 different occasions has also demonstrated the same (13) (14).

After initial stabilization, most of the patients in our cohort had an expected course of treatment during the remaining part of the induction chemotherapy. Out of the 11 patients, 3 patients abandoned treatment at various time points. Of the remaining 8 patients, 6 are alive and in remission at last follow-up. Treatment related mortality was noted in only 1 patient. The OS and EFS of the cohort was 75%. Morin et al. studied 50 patients with cancer and SVCS aged 25-59 years, median 37 years) and reported an overall mortality rate at 6 months of 48% (9). Tilak et al. in their study of 55 de novo T-LBL (age 3-36 years, median 18 years), have reported a 5-year OS of 59.8% (10). In a systematic review of pediatric SVCS cases by Nossair et al. the overall morbity and mortality was 30% and 18% respectively (15). In our study, 3/11(27%) patients abandoned treatment at various time points. Various other studies have also shown that treatment abandonment is a big barrier to improving outcomes for children with cancer in the developing world (16) (17). Treatment related mortality is also another major hurdle to improving the outcomes of pediatric oncology patients. In our cohort we lost one patient to treatment related complication.

Pediatric data of the presentation, course, management, outcome, and critical care needs of this cohort are limited, and it is difficult to approach such children safely. In our study, flow cytometry on peripheral blood and non-hematological fluids served as a valuable tool in diagnosing patients and prompt initiation of treatment. Despite the life-threatening initial presentations, timely initiation of specific therapy and effective critical care supportive treatment could improve the outcomes of this cohort.

Patients with SVCS, despite their life-threatening presentations of airway collapse, cardiac tamponade and shock, can have improved outcomes with good intensive care treatment and timely interventions. Utilizing flow cytometry for detection of blasts in peripheral blood/pleural fluid/pericardial fluid and delaying invasive procedures like bone marrow test and tissue biopsy in a clinically unstable child is a preferable option.

Disclosure – All authors have nothing to declare.

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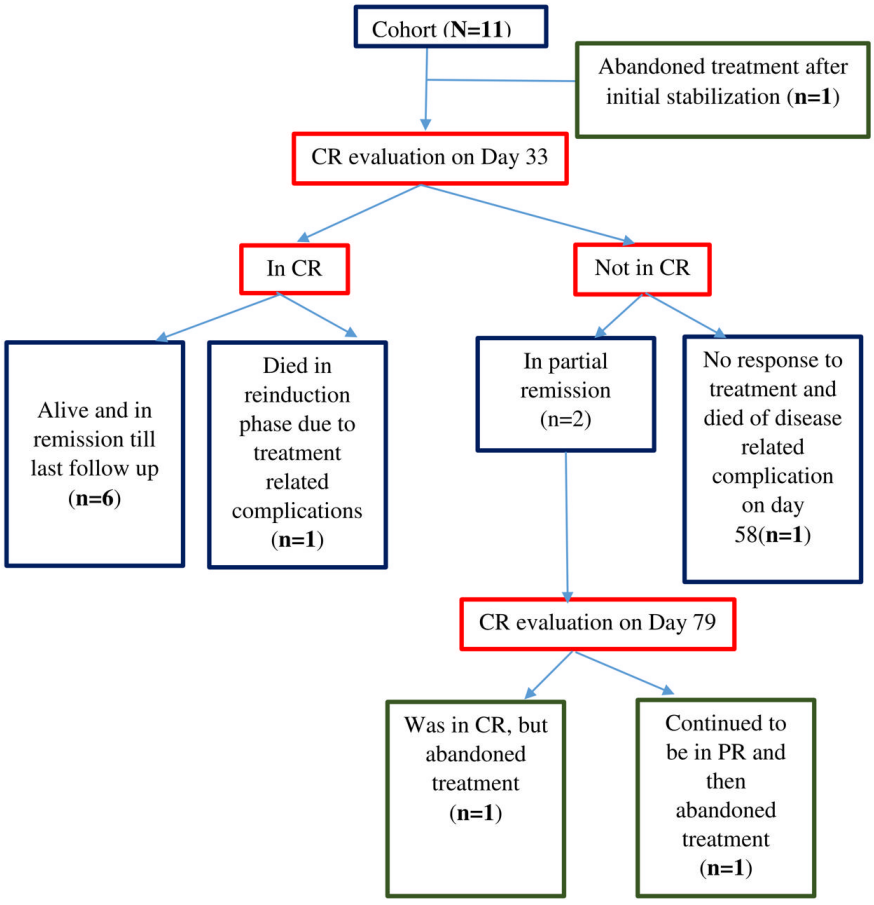
Legend

Fig 1. The follow-up and outcome of children with T cell leukemia/lymphoma with superior mediastinal syndrome



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