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Pleuropulmonary Blastoma: A Case Report and Review of Literature

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Abstract: ***Pleuropulmonary blastoma PPB is a rare, aggressive childhood cancer originating in the lungs or pleura. It progresses through three types I, II, III with increasing severity and is associated with DICER1 gene mutations. Clinical symptoms often mimic common respiratory infections, leading to misdiagnosis. Accurate diagnosis relies on imaging and histopathological examinations, with CT and PETCT scans providing crucial information. Treatment typically involves a multimodal approach, including surgery, chemotherapy, and sometimes radiotherapy. Early diagnosis and comprehensive management significantly improve survival rates, emphasizing the need for vigilant screening and follow - up, especially given the genetic implications of DICER1 mutations.***

Keywords: pleuropulmonary blastoma, childhood cancer, DICER1 mutation, multimodal treatment

1. Introduction

Pleuropulmonary blastoma (PPB) is a rare and highly aggressive malignant tumor of pleura or lung origin, often located in the lung periphery and invading the chest wall, mediastinum, thoracic vessels, lymph nodes, and diaphragm (1). It was earlier classified with pulmonary blastoma, which constitutes 0.25% - 0.50% of primary lung malignancies in all age groups (2). PPB is one of the more common types of primary lung malignancies in infants and children.

According to the stage of development, PPB is divided into three types, the earliest being purely cystic (type I), further progressing to mixed cystic - solid (type II), and finally solid (type III) (3). Another variant (type I - regressed - Type Ir) was added in 2006 (4). Type I tumors can progress with time to more aggressive type II and type III tumors. Moreover, pleuropulmonary blastoma is associated with mutation in DICER 1 gene and recognized as part of DICER syndrome comprising multiple other neoplasms (5). Thus, the correct diagnosis of pleuropulmonary blastoma and imaging surveillance to detect other commonly associated neoplasms is necessary (3, 4).

The clinical symptoms of PPB are atypical, in which children often present with shortness of breath or respiratory distress, flushing, and fever and are often mistaken for respiratory tract infections, pneumothorax, or pneumonia (6, 7). When children present with this lung inflammation - like condition, the routine imaging examination on admission is a chest radiograph. Chest radiographs often show reduced lung translucency, often misdiagnosed as pneumonia combined with the children's symptoms. Chest CT is helpful in the diagnosis of PPB but provides limited diagnostic information.18F - FDG PET/CT in pediatric oncology has been shown to have more benefits than drawbacks and is a more sensitive and specific diagnostic tool for evaluating pediatric malignancies (8).

The 5 - year survival rate of PPB is significantly related to the type, with 91% for type I, 71% for type II, and 53% for type III (5).

2. Case Report

A 18-year-old young male child was brought to the Out Patient Department of J K Cancer Institute with complaints of chest pain, difficulty in breathing and low grade fever for past 6 months which had been progressing over the last 2 months. The child also had complaints of weight loss and decreased oral intake for 1 month. Her previous medical and family history was unremarkable.

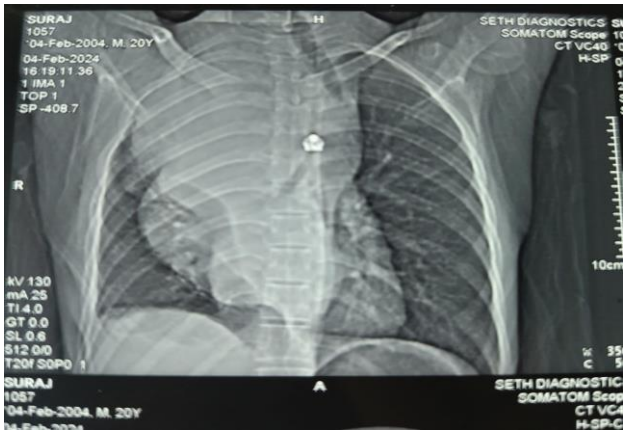
Clinical examination revealed that there was significant reduced air entry on right side with respiratory distress and absent breath sounds in right hemithorax. Trachea deviated towards left side. No past history of any chronic illness or developmental delay was present.

His hemogram reports showed a higher than normal white blood cell count (22.3×109/L). Chest X ray showed radio - opaque mass lesion in the right upper lung zone with broad base towards mediastinum. The lateral border of the mass and its interface with lung was ill defined. There was marked tracheal deviation and mediastinal shift to the left side. No obvious rib erosion, vertebral destruction or chest wall involvement was noted

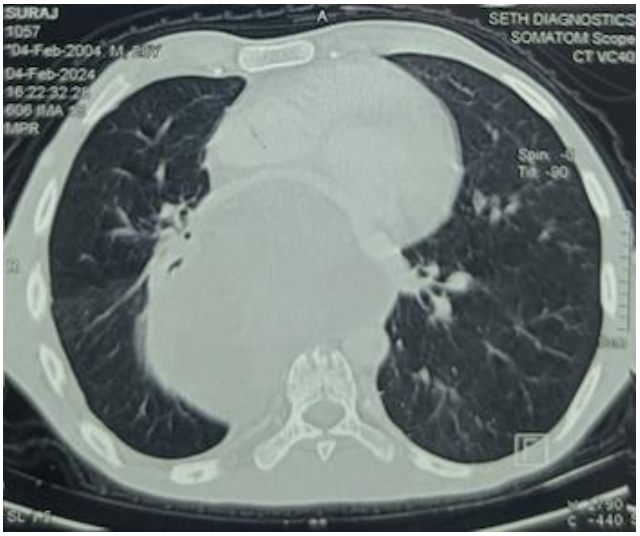
Contrast enhanced CT scan of thorax shows that Heterogenous soft tissue density mass lesion in the right side of superior mediastinum predominantly along right paratracheal region extending in right upper lobe of lung parenchyma approximately 120×102 mm in axial and 130 mm in craniocaudal extent. Contiguous extension of mass lesion is seen in posterior mediastinum and subcarinal region approximately 120×76 mm in axial and 93 mm in craniocaudal extent and extending in apical segment of right lower lobe of lung parenchyma. Few hyperdense haemorrhagic area are noted within the mass lesion. Mild to

moderate degree of heterogenous contrast enhancement is noted within the mass lesion with necrotic area within it. Mass lesion is causing significant mass effect on mediastinal structure causing antero - lateral displacement of tracheal airway with chinked airway at places. Trachea is significantly compressed and displaced towards left side and also compression of superior vena cava with multiple tortuous collaterals in chest wall – SVC syndrome. It further causes displacement and compression of upper 1/3rd of oesophagus. Significant mass effect is also noted in the left atrium. No definite intraspinal extension of mass lesion is noted. Patchy atelectatic changes are noted in the basal segment of right lower lobe of lung parenchyma

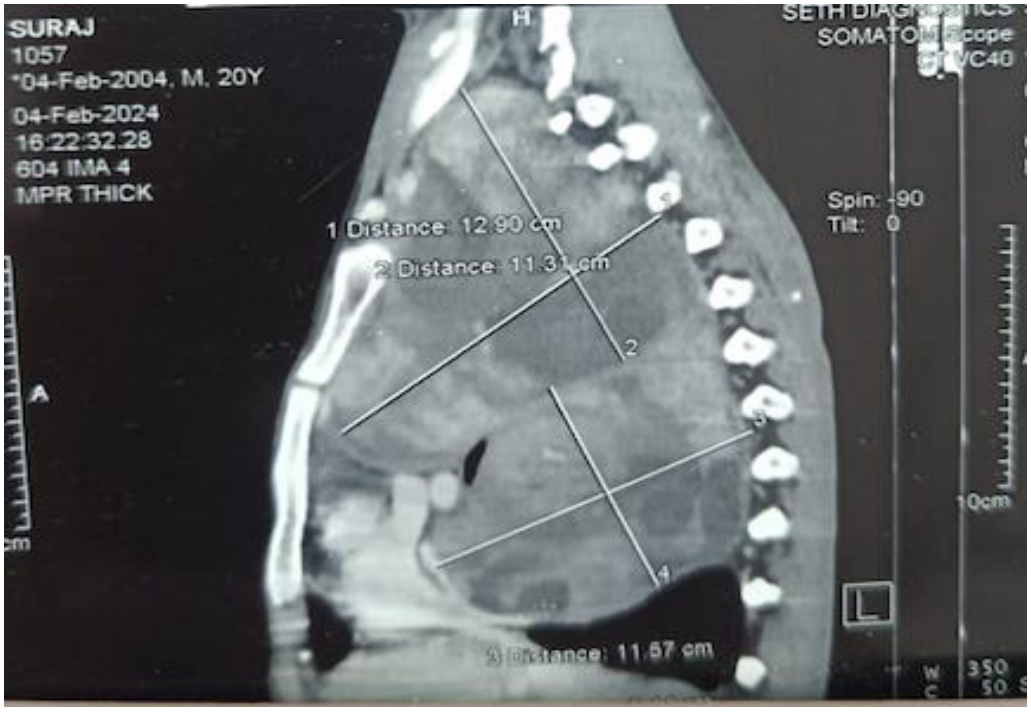
Based on the features of medial pleuropulmonary location of the mass lesion, no evidence of rib erosion, chest wall invasion or intraspinal extension, the provisional diagnosis of pleuropulmonary blastoma was made. Differential diagnosis of neuroblastoma was kept because of the posterior mediastinal location of the mass lesion



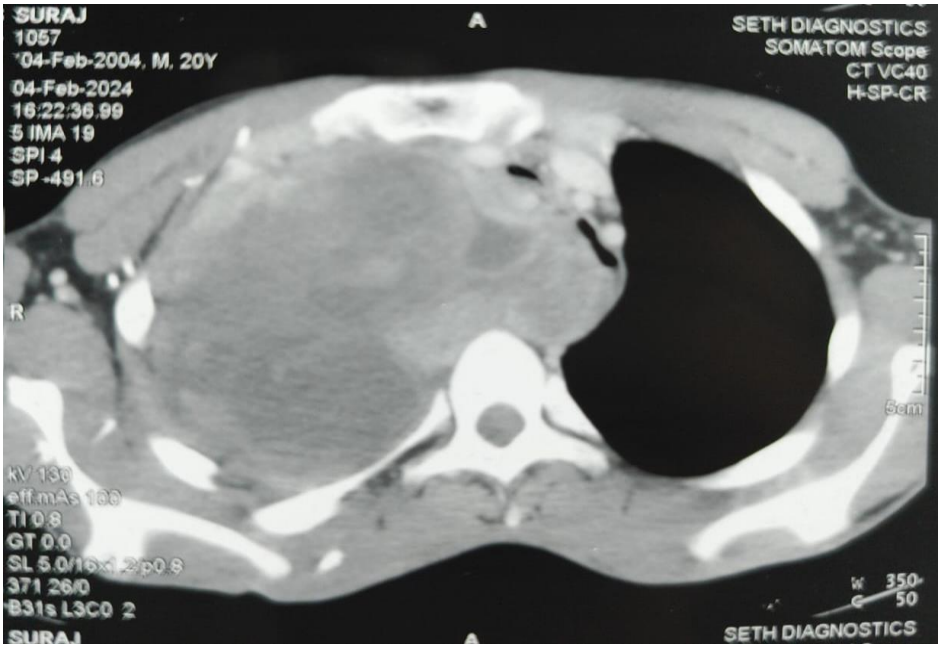
CT thorax shows incomplete homogenous opacification of right hemithorax with contralateral mediastinal and tracheal deviation



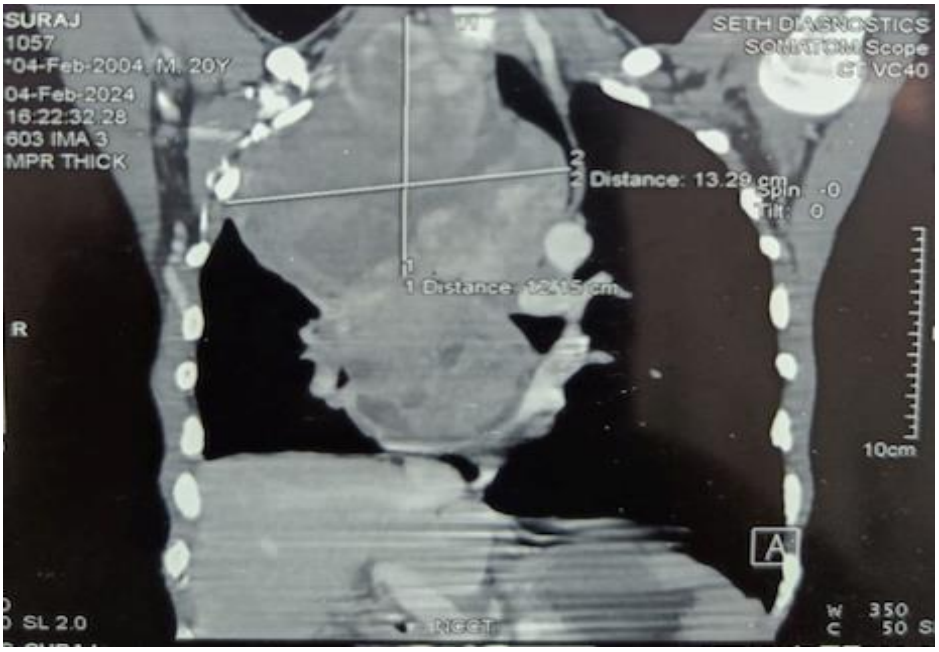
Axial lung window of CECT Thorax image shows compressed and collapsed oesophagus with splaying and compression of bilateral main bronchus



Sagittal image of CECT Thorax showed extension and mass effect of the mass on mediastinal structures and heart

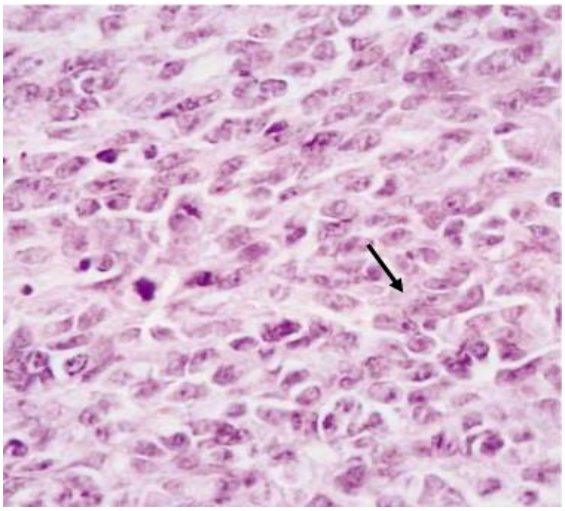


Axial image CECT Thorax showed a large well defined solid mass with heterogenous contrast enhancement with non - enhancing necrotic area in right hemithorax

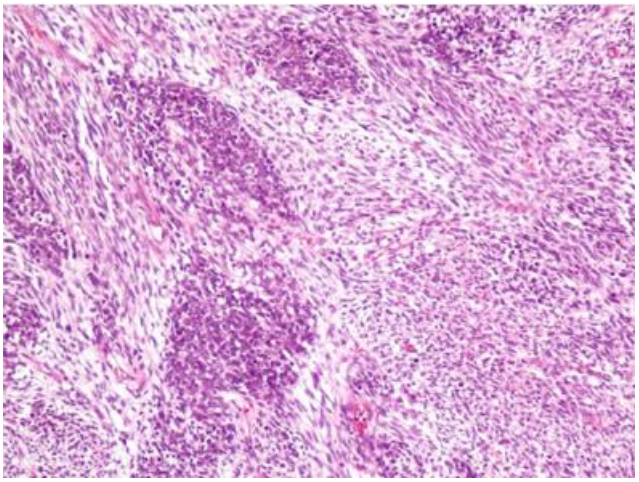


Coronal image of CECT Thorax shows large heterogenous contrast enhanced mass lesion with necrosis and displacement of mediastinal structure

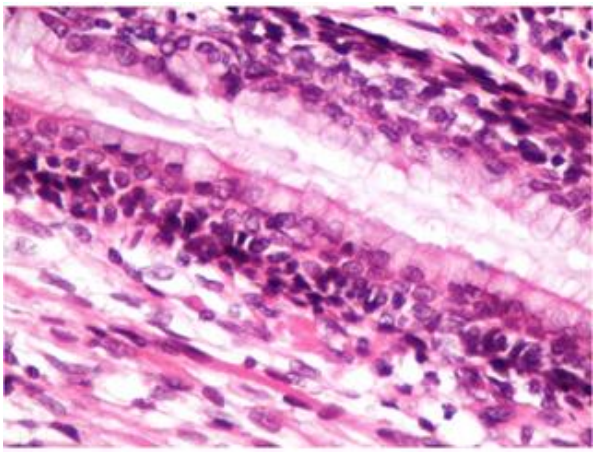
Fine Needle Aspiration of lung mass shows haemorrhagic smear with presence of monomorphic/mildly pleomorphic spindle cell. This spindle cell seems likely to be neoplastic. Further Tru - cut lung biopsy was done which shows a biphasic tumor made up of spindle cell and polygonal cells and primitive blastemal cells also seen which confirmed the diagnosis of pulmonary blastoma.



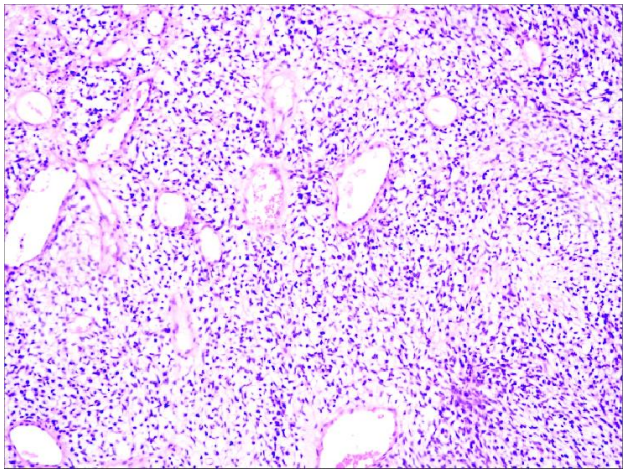
Solid portion of the PPB is composed of small primitive blastemal cell (malignant cells) without features of differentiation. The arrow indicates a mitotic figure of tumor cell (H&E, ×400).



Nodules of blastema like cells separated by loose tissue (H&E: ×100)



Microscopic cyst lined by ciliated cuboidal to columnar cells with subepithelial condensation of blastema - like to spindle shaped neoplastic cells (H&E:: ×200)



Blastemal cells with spindle, polygonal and round nuclei in the myxoid stroma

Initially patient treated symptomatically, then after planned for VAC regimen (Vincristine, Adriamycin Cyclophosphamide). After the completion of the first course of chemotherapy, dyspnea resolved, patient was stable and discharged in an ambulatory state. Patient was called for the second course of chemotherapy 3 weeks after the first cycle of chemotherapy

3. Discussion

Lung cancer in children are extremely rare, approximately 0.5–1% of primary lung cancer. PPB is the common pediatric primary intrathoracic malignancy, usually arising from either the lung or pleura. The majority of paediatric PPB present before 6 years of age (2). In 1961, Spencer first coined the term and suggested that the tumor is of mesodermal blastemal origin (10). In 1988, Manivel et al. described a specific subtype of pulmonary blastoma on the basis of its exclusive clinical presentation in childhood and its pathologic features of variable anatomic location, primitive embryonic - like blastoma and stroma, absence of a carcinomatous component, and potential for sarcomatous differentiation. It was also found that paediatric PPB type is distinct tumor from the biphasic epithelial stromal morphology of the classic adult type (9). In 2015, World Health Organization classified PPB as distinct from adult pulmonary blastoma and now falls under the category of mesenchymal neoplasms (11). According to International Pleuropulmonary Blastoma Registry, it is mainly of 3 types – type I, II, and III. These types form a continuum and there is progression from type I to type III over time (5, 12).

Median age for Type I is 8 months and the best prognosis among all types - 91% 5 - year overall survival rate. On histopathology, multiloculated cystic thin walled structure having fibrous septa with immature cells seen. Type I tumors carry the most favorable prognosis and account for 15% to 20% of all PPB. Type Ir (type I - regressed) is a subtype added in 2006, with a median age of 48 months and histopathological features of cystic areas with few spindle cells and foci of dystrophic calcification.

Median age for Type II is 35 months and 71% 5 - year overall survival rate. Solid nodules and polypoid tissue extending into cysts are seen in histopathology. Median age for Type III is 44 months and worst prognosis among all types – 53% 5 year overall survival rate. On histopathology it appears completely solid. Solid component in type II and III PPB contains mixed blastematous and sarcomatous elements which is different from adult type pulmonary blastoma (contains malignant epithelial and mesenchymal tissue). Type II and type III tumors behave aggressively and together (distributed equally) account for 80% to 85% of all PPB.

Certain genetic mutations are associated with pleuropulmonary blastomas; these include germ line DICER1 mutation (loss of function) in familial cases, gains of chromosome 8 (most consistent chromosomal abnormality), trisomy 2, unbalanced translocation between chromosomes 1 and X, and p53 mutations or deletions (16). Approximate 66 % cases with the malignancy have heterozygous mutation in DICER1 gene located on chromosome 14q13.2 (5). A total of 25% of cases have association with other neoplasms in

themselves or their families. . Various neoplasms associated with DICER1 syndrome include cystic nephroma, pineoblastoma, pituitary blastoma, ovarian sex cord stromal tumors, embryonal rhabdomyosarcomas and other tumors (13). Thus, screening is essential for a patient diagnosed with PPB for DICER1 mutation and associated neoplasms.

Clinical presentation is usually with nonspecific and its depend on the type of lesion such as respiratory distress, chest pain, hemoptysis, pleural effusion, pneumothorax (11). Others like, Fever, malaise and anorexia are associated with type II and type III PPB. On imaging, chest radiography is the first modality used for evaluation. PPB is more common on right side. It appears as hemi - opaque thorax with contralateral tracheal and mediastinal deviation (2). Other patterns are partial opacification of lung, benign appearing cystic lung disease, pleural effusion, tension pneumothorax and mediastinal shift (4). Contrast enhanced computed tomography of chest shows the morphology, enhancement pattern, complete tumor extension and invasion of adjacent structures. It include a single cyst, multi - cystic lesion, or solid lesions with or without an associated cystic component. These features help in differentiating pleuropulmonary blastoma from more commonly occurring lesions such as neuroblastoma, congenital pulmonary airway malformation (CPAM) and fetal lung interstitial tumor (FLIT).

Type I PPB appear as single cyst or multicystic lesions with fluid or air within. Type II PPB shows cystic lesion with air or fluid within and solid component which enhances on contrast administration. Type III lesions appear as heterogenously enhancing solid lesions with areas of hemorrhage or necrosis within (2, 4). Pleural effusion and pneumothorax can be commonly seen. Calcification is not a common feature. Approximately 9% of type II and III lesions present with metastasis, which are much less common in type I tumors. The most common sites of metastasis are the brain and bone and less commonly the liver. Because of the increased risk of metastatic disease in patients with types II and III, recommended evaluation for these patients includes an MRI of the brain and a bone scan (11).

The imaging modalities for staging in suspicion of PPB are contrast enhanced computed tomography of chest and abdomen (to detect cystic nephroma) for type I whereas, contrast enhanced computed tomography chest and abdomen, brain MRI, Bone scan for type II and type III pleuropulmonary blastomas (4).

PPBs require a multimodality treatment approach including surgery, chemotherapy, and radiation therapy (12). For large tumors, 2 to 4 courses of neoadjuvant chemotherapy is instituted to reduce the tumor size usually by more than 90% followed by surgical resection. A close follow up after Type I PPB diagnosis might detect early recurrence if the parents do not favor adjuvant chemotherapy. For Type Ir tumors only follow - up but no chemotherapy is recommended. The various chemotherapy agents that have been used include vincristine, actinomycin D, cyclosphosphamide, doxorubicin, ifosfamide, etoposide, cisplatin, carboplatin, epirubicin, methotrexate, and 5 - fluorouracil. However, no specific association has been shown between the survival and the chemotherapy used (12). The recommended chemotherapeutic regimen are IVADo regimen (ifosfamide, vincristine, actinomycin D, and doxorubicin) and VAC regimen (vincristine, actinomycin D, cyclophosphamide). For the usual type II and type III tumors, the treatment consists of aggressive surgery and chemotherapy. Because the response to chemotherapy is poor, some authors suggest that chemotherapy should be given with local radiotherapy in the majority of the patients. Resection followed by multimodal neoadjuvant chemotherapy and radiotherapy is the treatment of choice in more extensive disease with dissemination (15). Radiation therapy is reserved for nonresectable tumors or for residual tumors after chemotherapy. The most important prognostic factor is the total excision of the mass with clear margins. For brain metastasis, the recommended treatment consists of all three modalities, that is, surgery, radiation therapy, and chemotherapy in an attempt to achieve cure. For recurrent tumors high dose consolidation therapy (HDCT) with autologous stem cell rescue (ASCR) is recommended (4).

4. Conclusion

PPBs are primitive dysodontogenic or embryonic neoplasms of infancy and early childhood. Their occurrence beyond the first decade of life is a rare presentation. The supporting features for a diagnosis of pleuropulmonary blastoma are right sided mass lesion, complete hemithorax opacification, absence of intralesional calcification, no evidence of chest wall invasion/rib erosion/intraspinal extension. It is usually present with respiratory complaints with no specific radiological features on imaging. PPB is divided into subtypes correlates to the age of diagnosis and patient prognosis. Combining imaging and histopathological examinations should help in determining the diagnosis of PPB. Prompt recognition and differentiation from other benign congenital malformations or cystic lesions or other tumors are necessary to initiate treatment as soon as possible. The radical resection of the mass and the absence of metastasis are favourable prognostic factors. The patients diagnosed with the malignancy should undergo radical surgery, even in cases with microscopic residual disease. Multimodality treatment approach helps in ensuring satisfactory clinical results and increasing the survival of patient. Because of PPB associated with DICER1 syndrome, diagnosis of PPB should lead to screening and surveillance for commonly associated neoplasms such as cystic nephroma in the patient, their siblings and their first degree relatives.

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