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GIANT CELL PNEUMONIA IN CHILDHOOD*
(Report of seven cases emphasizing histopathological findings and associated conditions)

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Giant cell pneumonia (Hecht's pneumonia) is a rare entity which usually develops in patients with a disturbed immunological function of either congenital or acquired origin. It is more prevalent in childhood and is usually diagnosed through the main histopathologic findings, namely multinucleated giant cells.

It was towards the end of the 19th Century that some authors noted peculiar histological changes in the lungs of children who had died of measles. Kromayer[1] first suggested that this type of pneumonia might be diagnostic of measles, but it was Hecht[2] who found that there was a definite relationship between measles and the giant cells occurring in the involved lungs, which is the characteristic histopathologic finding of the pneumonia named after him. In cases of giant cell pneumonia an interesting point is the non-existence, or the short duration, of the characteristic measle rash[3,4]. Since the recognition of this fact, histopathological findings in the diagnosis of the disease[5] have been very important.

Giant cell pneumonia develops as a reaction of the host's inability to attain specific antibody response against the measles virus. Reticuloendothelial and some hematopoietic disorders, the usage of antimetabolites and the primary immune deficiencies, are the main predisposing factors. In these conditions, since the measles specific antibody production is impaired, a fatal disease of severe course occurs[5]. In these cases the diagnosis can usually be made at postmortem.

Because measles is still a major cause of death in children and because there is an increased use of immunosuppressives in various disorders, giant cell pneumonia has become a disease which is not infrequently encountered by pediatricians, even in

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developed countries. In this study we would like to draw attention to this peculiar disease by presenting the clinicopathologic features of the seven cases diagnosed in our center, in respect to the following:

(i) the frequency of Hecht's pneumonia in our autopsy series,

(ii) the pathologic changes in lung and lymphoid tissues,

(iii) the underlying diseases.

Material and Methods

In this study seven cases of giant cell pneumonia, diagnosed among the necropsies examined over the last ten years, are reevaluated. Complete postmortem examination material was available in six cases and some material (including lung, kidney, liver, skin and muscle tissue samples) in one. The material for light microscopic study was fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin (HE). Additional sections were prepared, as necessary. Feulgen stain was used for better demonstration of inclusion bodies. In one case only (no. 7), direct immunofluorescent study for demonstration of measles antigen in the lung, was performed. Clinical findings were obtained from the case records. To determine the incidence of giant cell pneumonia as compared with other types of pneumonia in the necropsy series, the pathology file was utilized.

Results

Clinical findings

The series was found to contain seven cases of giant cell pneumonia. All were in the under seven age group. Pertinent clinical data of the cases are given in Table I. The predominance of males to females was striking, the ratio being 5:2. A history of exposure to measles was obtained in four, and rash or contact with measles was absent in the remaining three cases. The interval between the rash and the development of pneumonia is seen to vary from ten days to two months. Fever and respiratory distress were the main complaints and in all cases crepitant or sibilant rales were audible on admission to hospital. The chest X-rays of all patients showed diffuse parenchymal infiltration (Figure 1). Case 3 also had radiologic findings consistent with tuberculosis.

As regards the underlying and/or coexisting diseases, four of the patients had congenital thymic dysplasia, due to which Case 1 developed generalized cytomegalic virus (CMV) infection, Case 2 had bronchitis and bronchiolitis, Case 3 had miliary tuberculosis with cavern formation and Case 4 had pulmonary abscesses, salmonellosis and cryptococcosis. As for the other three cases, Case 5 had abdomi-

TABLE I

Some Clinical Features of Patients with Giant Cell Pneumonia.

Case no. Initials	Age	Sex	Primary disease(s)	Interval between measles rash, if any, and onset of pneumonia	Duration of pulmonary symptoms	Type of pulmonary infiltration in chest X-ray
1 M.Y.	10 months	F	Thymic dysplasia	10 days	7 days	Diffuse
2 D.T.	3 years	M	Thymic dysplasia	22 days	22 days	Diffuse
3 B.K.	20 months	M	Thymic dysplasia Miliary tuberculosis	No rash	70 days	Diffuse*
4 N.A.	10 months	M	Thymic dysplasia	No rash	22 days	Diffuse
5 Z.I.	2.5 years	F	Abdominal tuberculosis	No rash	2 days	Diffuse
6 H.B.	21 months	M	Diabetes mellitus	10 days	6 days	Consolidation in right middle lobe
7 I.L.	7 years	M	Hodgkin's disease	2 months	4 days	Diffuse

* There were also consolidations in left upper lobe, and right paratracheal lymphadenopathy.

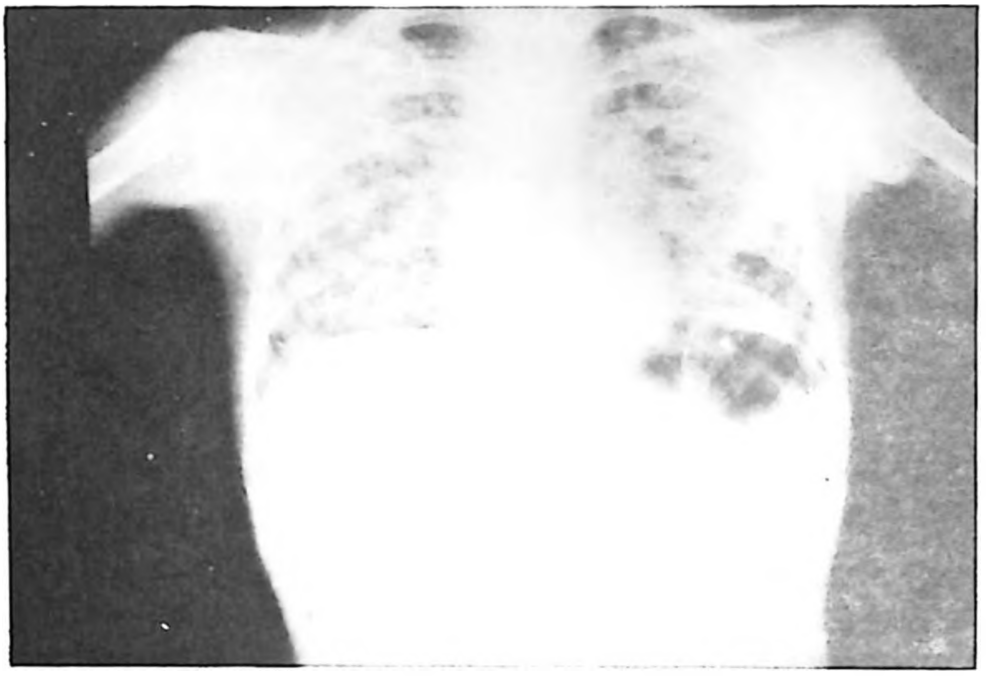

Figure 1.

Chest X-Ray of Case 7, showing diffuse granular infiltration.

nal tuberculosis, Case 6 had diabetes mellitus along with renal papillary necrosis and pyelonephritis and, finally, Case 7 had Hodgkin's disease, in remission under heavy chemotherapy.

Pathological findings

Macroscopically the lungs were generally enlarged. A firm consistency and a deep red to reddish-blue discoloration on cut surfaces was noticed in some. In other cases there were palpable infiltrates with a diameter varying from a few millimeters to one centimeter and a color varying from grey to greyish-yellow, giving the surface a miliary appearance.

Histologically, the microscopic changes were related to bronchitis, bronchiolitis, alveolitis and interstitial infiltrates (Figures 2 - 4). Squamous metaplasia of the bronchi (Figure 5), one of the other diagnostic features of giant cell pneumonia, was present in six of the cases. The majority of the cases revealed interstitial pneumonia with mononuclear cell infiltration. The multinucleated giant cells in the bronchioli and alveoli, which were the dominating microscopic finding, had a focal arrangement with the greatest concentration around the bronchioli. Giant cells, which were not encountered in non-infiltrated areas, appeared to be round to spherical or half-moon in shape. The nuclei, most of which were hyperchromatic and bearing eosinophilic inclusions, were generally located centrally, with a shape varying from round to ovoid (Figure 6). Intranuclear inclusions bearing multinucleated giant cells

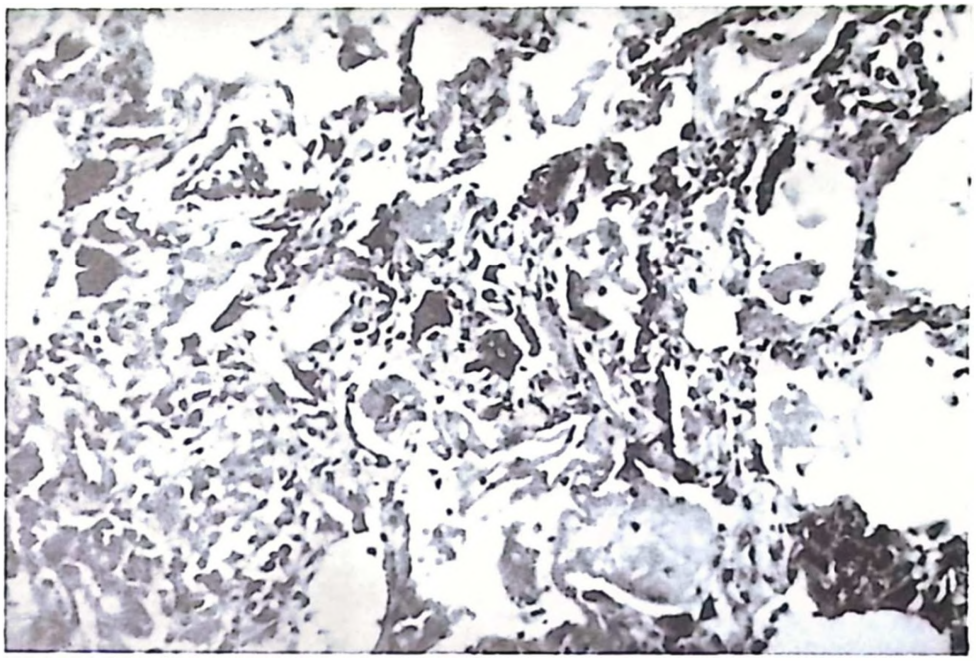

Figure 2.

Section of the lung showing multinucleated giant cells, clumps of fibrin and hyaline membrane-like formations (HE ×240).

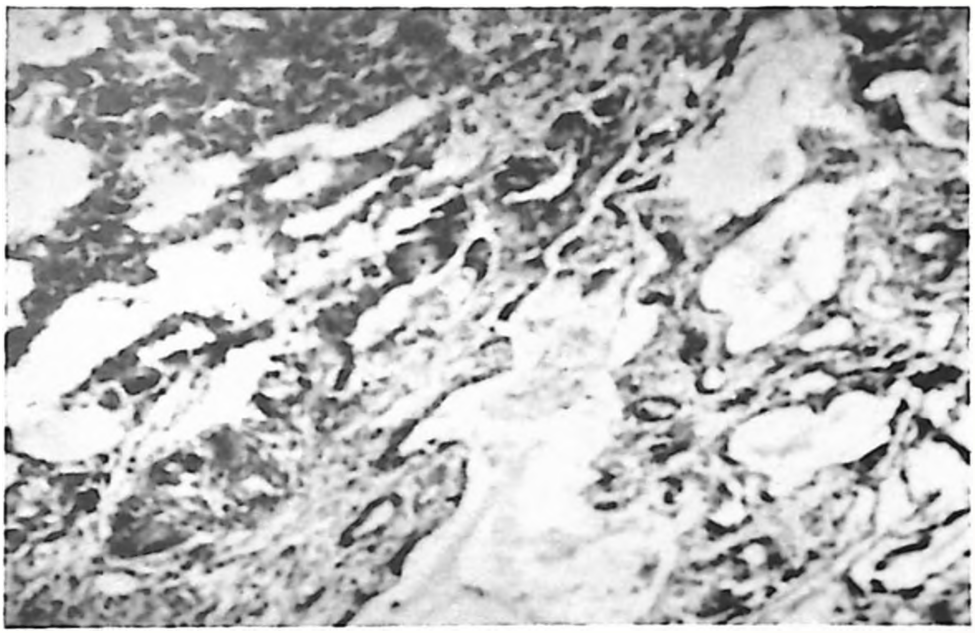

Figure 3.

Appearance of interstitial pneumonitis along with numerous giant cells lining alveoli and forming clumps (HE×150).

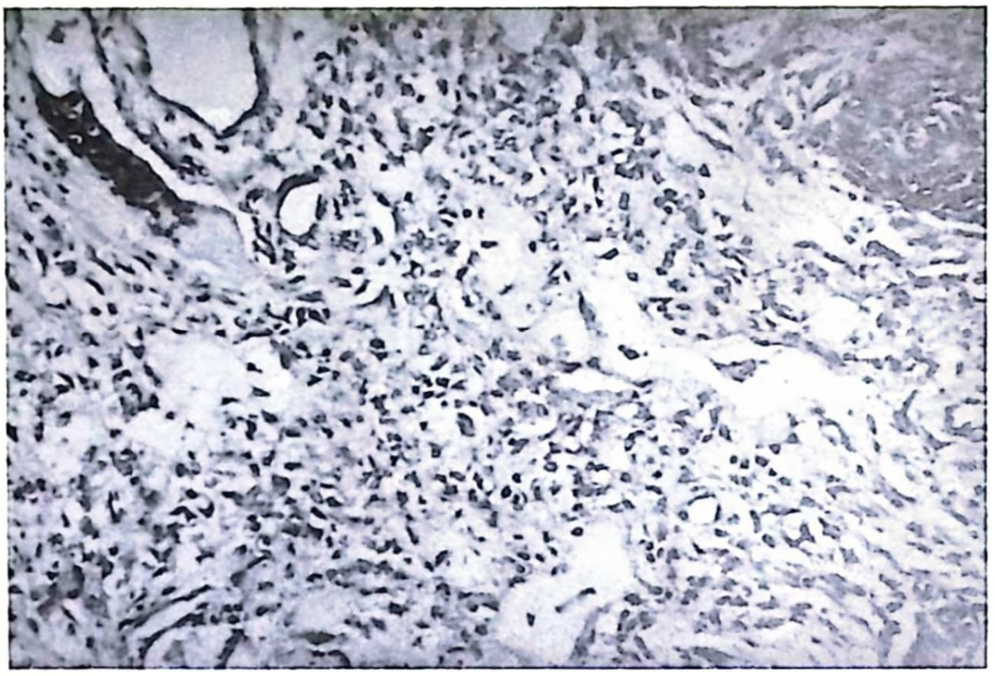

Figure 4.

Obstruction of the alveolar spaces due to organized pneumonia. A large giant cell on the left with evidence of early calcification and an island of clumps of epithelial-type cells on the right (HE × 175).

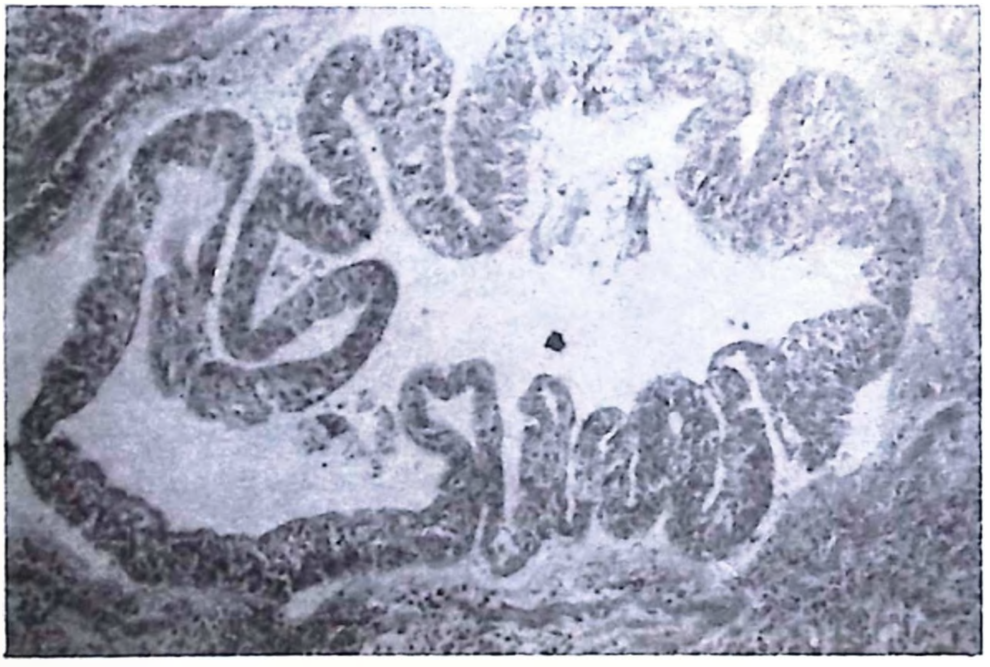

Figure 5.

A bronchus showing squamous epithelial metaplasia with scattered giant cells (HE × 175).

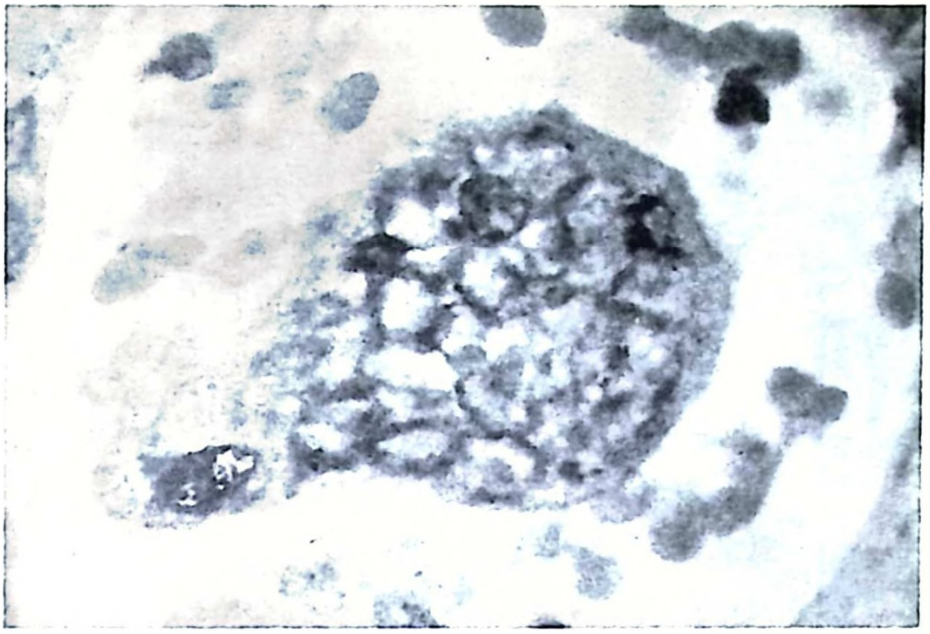

Figure 6.

An ovoid shaped giant cell bearing numerous intranuclear and a few cytoplasmic inclusion bodies in the alveolar space (HE×280).

were present in all of the cases, whereas intracytoplasmic inclusions were seen in only three cases (Table II). The majority of the epithelial-type giant cells were seen in alveolar spaces, occasionally in the bronchial and laryngeal epithelium and very rarely in the mucous glands.

The histopathologic features of the thymus and lymphoid tissues of these cases (Figures 7, 8) are summarized in Table III, where the presence of the giant cells is emphasized.

Warthin-Finkeldey cells were found in the lymphoid tissues of two cases. Many of the lymph nodes showed a high degree of prominence of reticulum cells and marked lymphocytic cell depletion in the paracortical region (Cases 1, 2, 3, 5 and 7). In addition, in some of these cases, there were relatively few lymphocytes or germinal centers in the primary follicles. There was diffuse caseation necrosis in Case 3 and necrosis with hyalinization in Case 7. The thymus was dysplastic in four, involuted in two and was not available for examination in one (Case 7). The absence of corticomedullary differentiation and the depletion of the lymphocytes of the thymus was conspicuous through cases one to six. Hassall's corpuscles were present in one, rare or absent in the other five of which Case 6 showed additional calcification.

Generalized cytomegalic virus (CMV) infection, miliary tuberculosis, and salmonellosis together with cryptococcosis were diagnosed postmortem in Cases 1, 3 and 4, respectively, in addition to thymic dysplasia.

TABLE II

Morphologic Findings of Patients with Giant Cell Pneumonia

Case no. Initials	Age	Sex	Site of inclusion bodies in pulmonary giant cells		Giant cells in lymphoid tissue	Bronchial metaplasia	Other findings at necropsy
			nuclear	cytoplasmic			
1 M.Y.	10 months	F	+	+	+	–	– Thymic dysplasia – Desquamative type pneumonitis with giant cells – Generalized CMV infection – Lymphocyte depletion in lymphoid tissue.
2 D.T.	3 years	M	+	–	+	+	– Thymic dysplasia – Lung: bronchitis, bronchiolitis, interstitial pneumonitis, pulmonary edema, multiple fibrin thrombi with giant cells – CNS: thrombi in dural sinus and cerebral veins
3 B.K.	20 months	M	+	–	–	+	– Thymic dysplasia – Miliary tuberculosis and cavern formation – Giant cell pneumonia

4 N.A.	10 months	M	+	+	–	+	– Thymic dysplasia – Lung: Multiple abscesses, giant cell pneumonia – Salmonellosis – Cryptococcosis
5 Z.İ.	2.5 years	F	+	+	–	+	– Thymic involution – Giant cell pneumonia – Abdominal tuberculosis
6 H.B.	21 months	M	+	–	–	+	– Thymic involution (atypical) – Giant cell pneumonia – Diabetes mellitus (clinical) – Pyelonephritis, papillae necrosis
7 İ.L.*	7 years	M	+	–	Not examined	+	– Hodgkin's lymphoma – Giant cell pneumonia – Severe lymphocyte depletion in lymph nodes.

CMV : Cytomegalovirus,

CNS : Central nervous system.

* Direct immunofluorescent study revealed staining with anti-measles antigen in the lung tissue

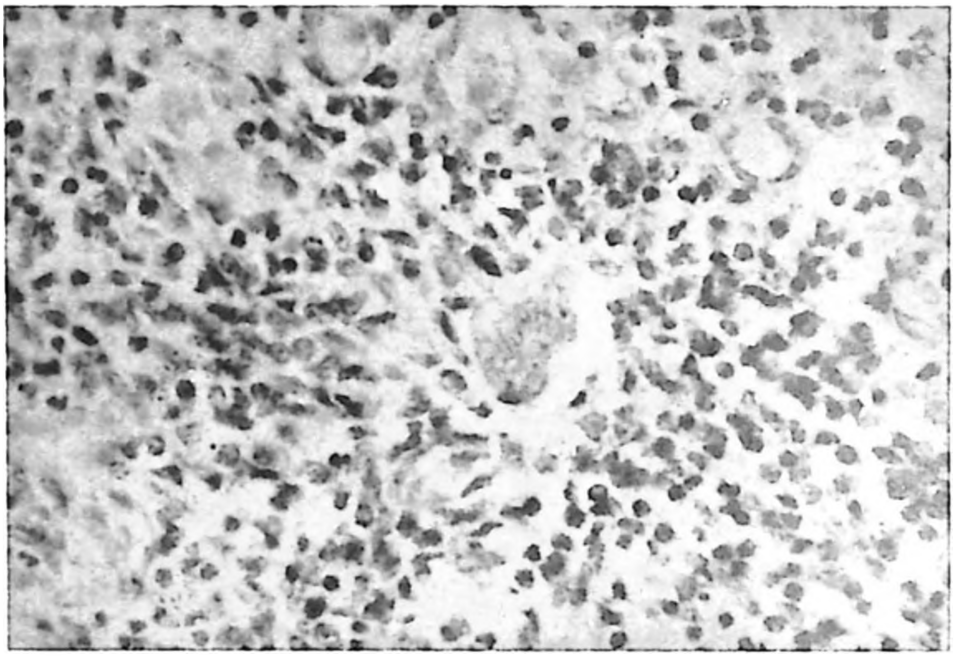

Figure 7.

A giant cell in the dysplastic thymus. The nuclear inclusion bodies are barely visible (HE × 200).

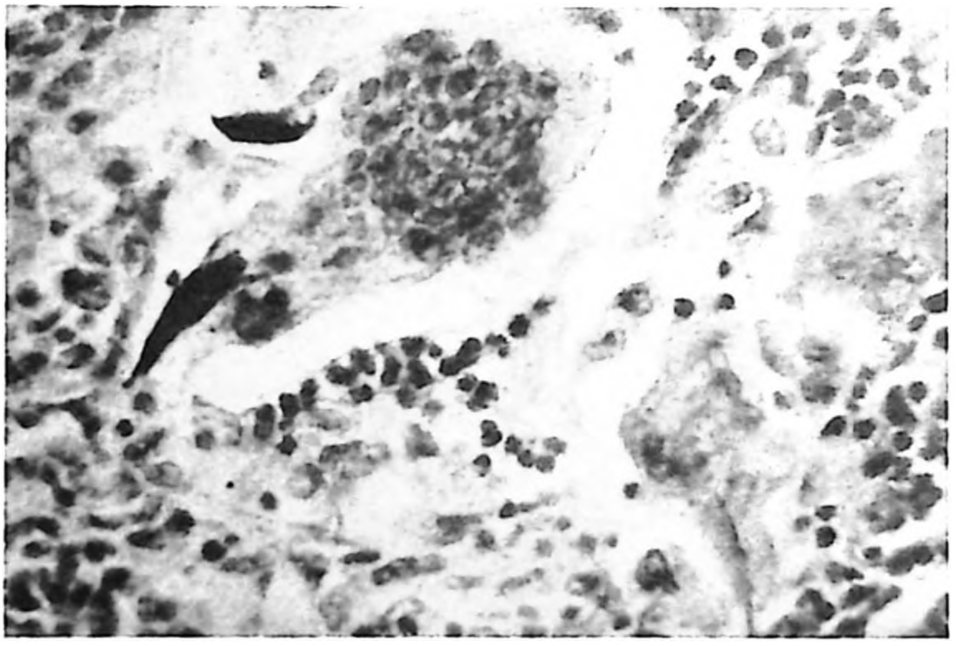

Figure 8.

Giant cells in the thymus, the largest one showing nuclear inclusions and evidence of calcification (HE × 325).

TABLE III

Histologic Features of Lymphoid Tissues of the Giant Cell Pneumonia Cases

Lymphoid Tissues	Cases as numbered						
Thymus	1 (M.Y.)	2 (D.T.)	3 (B.K.)	4 (N.A.)	5 (Z.İ.)	6 (H.B.)	7 (İ.L.)
– Cortex medulla differentiation	Absent	Absent	Absent	Absent	Absent	Absent	
– Lymphocytes	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Not examined
– Hassall's corpuscles	Absent	Very rare, abortive	Very rare, abortive	Absent	Present	Rare, calcified	
– Giant cells	Present	Present	Absent	Absent	Absent	Present	
Spleen							
– Malpighi bodies	Present	Rare	Present	Present	Present	Rare	
– Germinal center	Absent	Absent	Inconspicuous	Absent	Inconspicuous	Absent	Not examined
– Plasma cells	Absent	Absent	Absent	Absent	Absent	Absent	
– Interfollicular lymphocytes	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	
Lymph Nodes							
– Follicle	Present	Absent		Present	Present	Present	
– Germinal center	Absent	Absent		Rare	Rare	Absent	
– Plasma cells	Present	Absent	•	Present	Not definite	Absent	••
– Paracortical lymphocytes	Decreased	Decreased		Present	Decreased	Decreased	
– Giant cells	Absent	Absent		Absent	Absent	Present	
GIS Lymphoid Tissue							
– Follicle	Rare	Present	Rare	Rare		Rare	
– Germinal center	Absent	Absent	Absent	Absent	Not available	Absent	Not examined
– Lymphocyte	Decreased	Decreased	Decreased	Decreased		Decreased	
– Plasma cells	Present	Present	Present	Present		Present	

GIS: Gastrointestinal system.

• No evaluation possible owing to large areas of caseation

•• No evaluation possible owing to diffuse necrosis and hyalination

The measles antigen was demonstrated by the direct immunofluorescent technique in the giant cells in Case 7.

The incidence of giant cell pneumonia among the pneumonias in the necropsy series of the pediatric age group up to 14 years, newborns excluded, was found to be 3%.

Discussion

Giant cell pneumonia is a fatal disease and measles has etiologic significance. It is mainly a childhood disease and one which, until recently, has been encountered rather rarely. The increasing frequency of Hecht's pneumonia during recent years can be explained by the widespread use of steroids and cytotoxic agents in various conditions and by the fact that pathologists are gaining more experience with this entity, since it is almost always diagnosed postmortem. In an autopsy study of patients under 20 years of age, the incidence of Hecht's pneumonia among other pneumonias was found to be 8%[5]. In our pediatric center 3% of all pneumonia cases were seen to be of the giant cell type. It is thought that the relatively lower incidence of Hecht's pneumonia in our series is due to the predominance of bacterial pneumonias.

During measles viremia in the prodromal phase, the measles specific antibody is produced in patients with a normal immunological status; the viremia disappears after the rash becomes visible, and viral pneumonia does not occur, or if it does it is mild. However, in the case of immunocompromised children, either antibodies are not formed or an adequate level is not attained[7], there is generally no rash response[3] and the viremia continues[7] leading to Hecht's pneumonia, which terminates in death from anoxia[6] after two or four weeks.

The measles virus has long been thought to be responsible for giant cell pneumonia. Enders and co-workers[3] recovered measles virus from the lung cultures of three children dying of Hecht's pneumonia. These children, who had leukemia, mucoviscidosis and Letterer-Siwe disease as underlying diseases, never developed the typical symptoms or exanthem of measles. In some reports there is an association made between giant cell pneumonia and leukemia[7,12,13]. Its occurrence is also reported in a child treated with cyclophosphamide for a steroid resistant nephrotic syndrome, and aggregates of microtubules, closely resembling the measles virus nucleocapsid in the nuclei of alveolar giant cells, are described[11].

Most of the clinical and pathological findings of measles in children with altered immune mechanism are different from the findings in children whose immune mechanism is intact. Of these, the pathological features will be emphasized as follows:

Some histologic findings of measles in children with intact immune mechanism: Two types of multinucleated giant cells have been described in children with a normal immune mechanism who develop measles:

a) reticuloendothelial giant cells (Warthin-Finkeldey giant cells) and

b) epithelial giant cells[8,9].

The reticuloendothelial giant cells are large multinucleated giant cells and usually have numerous nuclei (up to 50) packed into a grape-like cluster in a scanty cytoplasm and first observed independently by Warthin and Finkeldey in tonsils. Later, they were observed in various lymphoid tissues such as the appendix, intestinal lymphoid tissue, lymph nodes (peribronchial, retroperitoneal, peripancreatic), thymus, spleen and bone marrow. These cells are to be seen in prodromal measles, as early as five days before the appearance of the rash and generally disappear within two to four days after the onset of the exanthem[8-10].

Epithelial giant cells are frequently found in the tracheobronchial tree and alveoli where they predominantly affect the respiratory epithelium[8]. These epithelial giant cells have numerous nuclei (frequently more than 30 per cell) and abundant pink cytoplasm. Eosinophilic inclusion bodies, both in cytoplasm and nuclei, are frequently noted. It appears that these types of giant cells are formed by fusion of the epithelial cells[9,11]. The epithelial giant cells disappear shortly after the onset of the measles rash.

Some histologic findings of measles in children with an altered immune mechanism: In addition to alveolar epithelial giant cells and tracheobronchiolitis, metaplasia of the bronchial epithelium, mononuclear cell infiltration and bacterial superinfection are known to occur in Hecht's pneumonia. This peculiar giant cell pneumonia is now known to occur in children with underlying diseases of the reticuloendothelial or the hematopoietic systems and those treated with antimetabolites[6,7].

The histologic diagnosis of Hecht's pneumonia is based on the finding of the characteristic epithelial type of multinuclear giant cells in the lungs. The demonstration of eosinophilic, intranuclear and intracytoplasmic inclusion bodies in the giant cells is of great importance.

Even though inclusion bodies may be encountered in viral pneumonias caused by adenovirus, cytomegalic, parainfluenza and varicella viruses, multinuclear giant cells with eosinophilic, intranuclear and intracytoplasmic inclusion bodies in the peripheral respiratory tract in man appear to occur exclusively with the measles virus, and the inclusions contain specific virus antigens[5]. In an electron microscopic study the similarity between intranuclear inclusion bodies and the measles nucleocapsid has been shown[14].

The characteristic measles rash either does not appear or is of very short duration in patients diagnosed as having Hecht's pneumonia[3,5]. If the exanthem is regarded as an index of cellular immunity, this peculiarity may be regarded as an indication of the depression of the immunological functions whether this be of congenital or acquired origin. Four of our cases had thymic dysplasia. As is known, hypoplasia with dysplastic feature of the thymus and congenital defect of cellular and humoral immunity are the main features in thymic dysplasia. The depletion of lymphocytes and the absence of follicle formation and germinal centers in non-thymic lymphoid tissues is due to a defect at stem cell level. Histologically, all of our thymic dysplasia cases revealed similar findings in the lymphoid tissues (Table III). The generalized cytomegalovirus infection, the miliary tuberculosis, and the salmonellosis and cryptococcosis as seen in Cases 1, 3 and 4 are the types of infection seen in combined immune deficiencies. Further, in association with the giant cell pneumonia, there is intra-abdominal tuberculosis in one patient (Case 5) and diabetes mellitus in another. Pyelonephritis and renal papillary necrosis, as a complication of diabetes mellitus, were also present in Case 6 in addition to giant cell pneumonia. The type and chronicity of the diabetes and tuberculosis could have played a role in the disturbed architecture of the lymphoid organs (mainly in the peripheric lymphoid tissue) resembling that found in immunodeficiency. Although the appearance of the central and peripheric lymphoid tissue was indicative of immunologic depression, it has not been possible to say whether it was of acquired or congenital origin. Abnormal reticuloendothelial system function and reduced T-lymphocyte and B-lymphocyte activity in diabetes mellitus have been reported in the literature[16]. Consequently, the occurrence of giant cell pneumonia in the case of diabetes mellitus interested us considerably, since to our knowledge this disease has not previously been suggested in the literature as a predisposing condition for the development of Hecht's pneumonia.

The clinical course of giant cell pneumonia is usually severe, and after the onset of acute and pronounced dyspnea and cyanosis, death may ensue in a short period of time. In the study presented, the duration of pulmonary symptoms before death varied from two to twenty-two days in six cases and continued for 70 days in the case of the patient with miliary tuberculosis, for which he received both intensive specific and non-specific therapy.

Though trials of treatment of this disease have been disappointing, the beneficial effect of administering high-dose gamma globulin in inhibiting the viremia and thereby hindering the dissemination of measles, is stressed in various reports[5,12]. The significance of prevention of exposure to measles of immunocompromised children is clear. Children not immunized before developing a malignant disease may have difficulty in resolving the measles infection, as evidenced by the persistence of virus isolation after the early stages of the exanthem and the delayed anti-

body rise. This might contribute to the extremely variable period between the onset of clinical measles and the development of giant cell pneumonia.

With the current drop in the immunization status of our pediatric population, there will undoubtedly be a rise in the number of cases of measles and measles pneumonia among unimmunized and immunosuppressed patients. In dealing with a patient who has both measles and a malignant disease we suggest the following:

1. A child who has been adequately immunized or contracted measles before receiving anti-tumor therapy should be considered to be at little or no risk.
2. In the case of unimmunized and immunosuppressed patients at risk, give a prophylactic injection of gamma globulin at the first evidence of a measles' epidemic in the area or at the time of exposure.

Summary

Giant cell pneumonia is an atypical fatal measles infection affecting children with altered immunologic status and is usually diagnosed postmortem by demonstration of multinucleated giant cells. Seven pediatric cases of Hecht's pneumonia, which account for 3% of all pneumonia cases in the ten-year Hacettepe pediatric necropsy series, have been diagnosed by light microscopic examination. In addition, in one case, the measles antigen was demonstrated in a direct immunofluorescent study. In three cases there was no clinical evidence of measles. As an underlying disease and/or associated condition, there was thymic dysplasia in four patients, tuberculosis in two and one case each of diabetes mellitus and Hodgkin's disease (in remission under heavy chemotherapy). Clinical features and pertinent histopathologic findings of the lungs and the lymphoid tissues of the patients are mentioned. The increasing frequency of giant cell pneumonia in patients with altered immunologic status is stressed, the literature concerning the cytopathologic changes specific for measles is briefly summarized, and suggestions for the prevention of this fatal disease are made.

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