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Varicella Pneumonitis

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Four adults had varicella pneumonitis. All developed respiratory symptoms within a week of the exanthem. Cough and/or dyspnea, cyanosis and chest pain were common. Radiological signs of disease were more marked than physical signs. A slight polymorphonuclear leukocytosis and normal sputum culture were usual. One man with mild symptoms recovered. Two women, one pregnant, had severe symptoms and died. A second man succumbed to secondary bacterial pneumonia. The lungs in fatal cases showed interstitial pneumonitis with mononuclear cell infiltrate, focal areas of necrosis, and acidophilic inclusion bodies in two cases. Patients received oxygen, antibiotics and, in one instance, corticosteroid therapy. The value of antibiotics and corticosteroid treatment is questionable. Use of gamma globulin in preventing varicella pneumonitis is mentioned and residual pulmonary changes are discussed.

Il s'agit de l'observation de quatre malades souffrant de pneumonite post-varicelleuse. Chez tous, les symptômes respiratoires se manifestèrent une semaine après l'exanthème. La toux, la dyspnée, la cyanose et une douleur thoracique étaient des symptômes courants. Les signes radiologiques étaient plus marqués que les signes somatiques. On trouvait d'habitude une légère leucocytose polymorphonucléaire et une culture normale des crachats. Un malade du sexe masculin, dont les symptômes étaient bénins, guérit. Deux femmes, dont l'une était enceinte, présentait des symptômes graves et moururent. Un deuxième malade mâle succomba à une pneumonie bactérienne secondaire. Dans les cas fatals, les poumons révélaient une pneumonite avec infiltration de cellules mononucléaires, des aires focales de nécrose et inclusions cytoplasmiques acidophiles dans deux cas. Les malades ont été traités au moyen d'oxygène d'antibiotiques et, dans un cas, de corticoïdes. La valeur thérapeutique des antibiotiques et des corticoïdes est douteuse. L'auteur a exposé la possibilité d'employer la globuline gamma pour prévenir la pneumonite post-varicelleuse et les modifications pulmonaires résiduelles.

MOST cases of chickenpox occur in children. The disease is usually characterized by relatively mild systemic symptoms, a vesicular exanthem and a benign course. Adults are infected less commonly. They may develop a more severe illness and seem prone to develop complications. In this report, four adults who developed varicella pneumonitis are presented. Three of the four died and their autopsy findings are included.

Case Reports

Case 1.—A 36-year-old farmer was admitted to hospital five days after contracting chickenpox from his 7-year-old daughter. He first complained of moderately severe backache. Within 24 hours he noticed lassitude and anorexia, and developed a fever of 102° F. Some red spots then appeared on his abdomen and were followed by crops of others until his trunk and limbs were covered. During the next three days the spots became, in succession, "a single clear bubble, then pus-like and finally dried up". While the skin eruption was spreading, the patient's eyes "itched and discharged a yellowish material". A high fever continued until the fourth day of his illness, when he noticed an increasing tightness in his chest which "cut him off" when he took a deep breath. He became very dyspneic, then orthopneic, and he wheezed. He developed a dry cough, but within 12 hours was coughing up pink, frothy sputum.

When examined in hospital he had a temperature of 102° F. The skin was covered with pearly-white, crusted lesions with erythematous borders, some red papules and a rare vesicle; the trunk was severely involved. The patient had bilateral conjunctivitis and small white vesicles with erythematous borders on the buccal mucosa and soft palate. Although he

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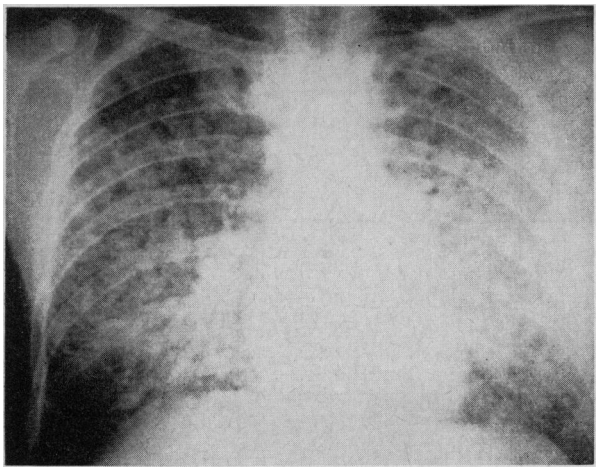

Fig. 1.—Posteroanterior chest radiograph (Case 1) on first admission, demonstrating bilateral nodular pulmonary densities.

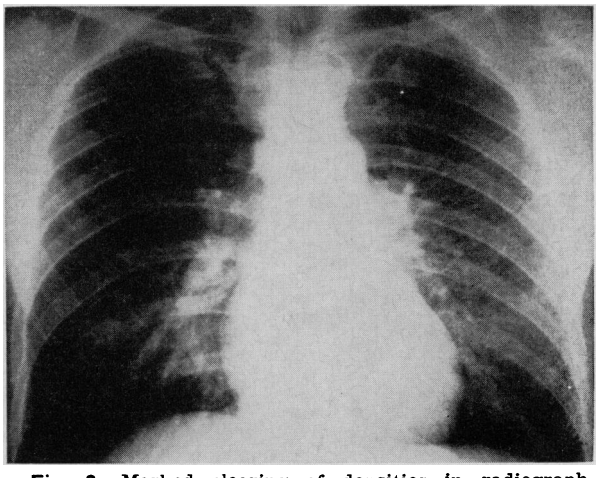

Fig. 2.—Marked clearing of densities in radiograph taken four days later (Case 1).

was sitting up in an oxygen tent, he was moderately dyspneic and had a persistent dry, hacking cough. The percussion note was dull at the lung bases. Fine rales were heard posteriorly and occasional expiratory rhonchi were heard throughout both lung fields. The blood pressure was 130/90 mm. Hg and the heart rate, rhythm and sounds were normal. The liver was tender and enlarged one fingerbreadth below the right costal margin. Neurological examination was normal.

The urine contained a trace of protein. The hemoglobin (Hb.) level was 14.1 g. % and the white blood count (WBC) 9500 per c.mm., with 60% neutrophilic leukocytes. The erythrocyte sedimentation rate (ESR) was 44 mm. in one hour; the Wassermann reaction negative. Neither serological studies for virus nor virus culture was attempted. No pathogenic bacteria were present in the sputum. Widespread patchy areas of consolidation were obvious throughout both lung fields in the chest radiograph (Fig. 1).

A diagnosis of varicella pneumonia was made, oxygen therapy was continued and tetracycline administered. Within three days, the patient's temperature gradually dropped to normal, he showed marked improvement and the radiological opacities in his lung fields cleared (Fig. 2). He was discharged from hospital five days after admission.

CASE 2.—A 35-year-old woman was infected with chickenpox virus by her daughter. A typical vesicular skin eruption appeared, accompanied by fever and general malaise. On the fourth day of her illness, the patient suddenly became cyanosed and dyspneic and died within two hours.

Postmortem findings.—An autopsy restricted to an examination of the heart and lungs was performed after the body had been embalmed. No vesicles were seen on the skin surface, but numerous pink ulcers with dried surfaces were present. The right lung weighed 700 g., the left 650 g. Dark red areas were scattered diffusely over the pleural surfaces, and were accentuated by the pallor of patches of normal lung in between. These dark red areas were circular, raised above the general surface and varied from 0.5 to 2.0 cm. in diameter. The cut surface of the lung showed similar congested areas scattered through the parenchyma.

Sections from the congested zones showed hemorrhage and small areas of alveolar wall necrosis, some related to small inflamed arteries. At the perimeter of the necrotic areas the alveoli were filled with an exudate of fibrin, monocytes and red blood cells and often lined by a hyaline membrane. Elsewhere the alveolar walls were thickened and infiltrated by mononuclear cells. Very few acute inflammatory cells were seen. A few large, round acidophilic intranuclear structures like viral inclusion bodies were seen in macrophage-like cells in the necrotic areas. The ulcers in the skin showed a mononuclear cell response, but balloon cells, multinucleate cells and inclusion bodies were not obvious.

CASE 3.—A 30-year-old woman developed chickenpox in the eighth month of her sixth pregnancy. Two of her children had had the disease 17 days earlier.

The patient complained of a dull sacral pain and developed a fever of 103° F. before a typical varicella skin eruption appeared. Without respiratory symptoms in the interim, she suddenly became cyanosed two days later. Her doctor found her unconscious and deeply cyanosed, and heard crepitations at the base of the left lung, but after the administration of oxygen the patient recovered consciousness. She was admitted to hospital and placed in an oxygen tent but had to be given additional oxygen by mask to maintain a normal skin colour. The next day, following a surgical induction of labour, she gave birth to a stillborn fetus which showed no stigmata of chickenpox. Later that day her respiratory difficulties increased, a tracheostomy was made, and she was placed on a Bird respirator and transferred to the Toronto General Hospital.

There, at the time of admission, she suffered a cardiac arrest.

Physical examination after successful resuscitation revealed vesicular skin lesions scattered profusely over the face, trunk and limbs, many of them hemorrhagic. Fine crepitations were heard at the lung bases posteriorly. The blood pressure was 160/100 mm. Hg. The heart sounds were normal and the pulse rate was 140/min. The liver was palpable three fingerbreadths below the right costal margin. The pupils were slightly dilated and responded sluggishly to light. Slow but equal knee jerks were the only reflexes elicited. The plantar response on both sides was equivocal.

The patient's Hb. was 13.3 g. % and the WBC 42,000 per c.mm. with 64% polymorphonuclear leukocytes. The count fell to 27,500 per c.mm. five days later. The ESR was 7 mm. in one hour. A trace of protein was the only abnormal finding in the urine. The arterial pH was 7.34, the carbon dioxide content of the blood 16.7 mEq./l. and the carbon dioxide pressure 30 mm. Hg. No pathogenic bacteria were found in the sputum. Chest radiographs showed extensive, symmetrical fluffy infiltrates in both lungs. These diminished in size during her stay in hospital.

The patient was cooled to between 91° and 93° F. and given sedatives, muscle relaxants, anticonvulsants and tetracycline. Three hours after the cardiac arrest she had a grand mal seizure and thereafter was in decerebration until her death seven days later. One attempt was made to discontinue the muscle relaxants and warm the patient, but mild seizures occurred and the relaxants and hypothermia were reinstituted. Five days before she died both legs became edematous owing to deep vein thrombosis, and in addition gangrene of the left leg and foot developed.

Postmortem findings.—Numerous dry eschars were scattered over the trunk and limbs. Many were surrounded by a hemorrhagic zone. The left lower leg was gangrenous from two inches below the knee, and thrombi were present in the left external iliac, femoral and calf veins. Presumably the arterial insufficiency was due to vascular spasm or to the compression of vessels and reduced arterial flow in the swollen limb. The right lung weighed 950 g., the left 760 g. The pleural surfaces of both lower lobes were studded with lesions which were red, 1-3 mm. in diameter and rimmed by a narrow white zone. Larger dark purplish congested areas were also apparent on the pleural surface and extended into the parenchyma. They did not correspond to any anatomical subdivision. The pituitary was large and soft. The brain weighed 1370 g.

Sections from the skin showed necrosis involving epidermis and superficial dermis with a mononuclear cell infiltrate and hemorrhage. Neither balloon cells nor inclusion bodies were apparent. In all parts of the lung, the alveolar septae were thickened and infiltrated by numerous mononuclear cells. Mononuclear cells, erythrocytes and edema fluid filled the alveoli which often showed hyaline membranes. The alveolar walls were necrotic in small areas; some of these were related to inflamed arterioles. Several degenerating mononuclear cells contained inclusion bodies. Areas of focal necrosis with an associated mononuclear cell infiltrate were seen in the pancreas. Sections from the pons, medulla, cerebellum and cervical spinal cord showed foci of cellular infiltrate, glial scars or a diffuse proliferation of elongated mesoglial cells. These changes were thought to be due to varicella encephalitis rather than to post-infection encephalitis. No viral inclusion bodies were seen in the brain nor was a virus culture successful. A number of recent infarcts in the pituitary were probably related to the cardiac arrest one week before death.

CASE 4.—A 55-year-old man was exposed to a child with chickenpox. Seventeen days later a hemorrhagic vesicular skin eruption appeared, and in four days spread to cover his body and limbs. Two days later, a brassy non-productive cough developed. The patient was treated with tetracycline and remained at home for a week. He had nocturnal fever of 102-103° F., became progressively dyspneic and began to experience right chest pain on deep inspiration. He was admitted to hospital.

When examined, he appeared critically ill. His body and limbs were covered with an extensive, confluent, crusted, hemorrhagic, maculopapular rash with an occasional flattened vesicle. The conjunctivae were injected and chemotic, and showed blotchy hemorrhagic lesions. Small ulcers were present on the posterior pharyngeal wall. The patient was orthopneic and tachypneic. His breath sounds were coarse and air entry of the lung bases was reduced. Rales could be heard in the infra-axillary regions of both lungs, particularly at the right base. The blood pressure was 140/70 mm. Hg. Heart sounds were normal.

The Hb. level was 13.5 g. %, and the WBC 6000 per c.mm., with a normal differential count. The ESR was 42 mm. in one hour. One of the vesicular lesions was smeared on a glass slide and when stained with Geimsa stain showed epithelial balloon cells, multinucleate giant cells and intranuclear inclusion bodies. However, the virus could not be cultured. The sputum contained a very light growth of *Pseudomonas aeruginosa*. In the chest radiograph, the right hemidiaphragm was elevated and bilateral mottled densities were concentrated mainly in the perihilar region.

The tentative diagnosis was varicella pneumonitis. Treatment consisted of 40 mg. prednisolone per day and a varying combination of penicillins and broad-spectrum antibiotics. As he had difficulty in maintaining normal blood gas levels, a tracheostomy was done and he received oxygen therapy. In the succeeding days his respiratory difficulties increased. Large amounts of mucopurulent material were aspirated from the tracheostomy and from this an increasingly heavy growth of *Pseudomonas aeruginosa* was cultured. Radiologically the pneumonitis progressed and cavities became apparent in some of the opacities. During this period a marked poly-

morphonuclear leukocytosis developed. The patient died 14 days after admission to hospital.

Postmortem findings.—The trunk and limbs were covered with crusted lesions 2-30 mm. in diameter, some with a hemorrhagic "base". No vesicles were seen. Each pleural cavity contained 100 ml. of bloody fluid. The right lung weighed 990 g., the left 1140 g. The pleural surfaces of both showed mottled dark zones with firm, congested parenchyma deep to them. Areas of hemorrhagic consolidation and of yellowish bronchopneumonic consolidation, some with abscesses, were seen on the cut surface, particularly in the upper lobes. The liver weighed 1930 g., and scattered over its surface and through the parenchyma were yellowish areas 0.4 cm. in diameter, surrounded by a reddish band.

Microscopically, the ulcers of the skin showed necrotic tissue, with a mononuclear reaction. No inclusion bodies were seen. In some parts of the lung, there was an interstitial pneumonitis with mononuclear cell infiltrate and occasional giant cells, but no definite viral inclusion bodies. Elsewhere, areas of acute bronchopneumonia with abscess formation were seen, some with organization. In the liver, areas of focal necrosis with an associated mononuclear cell response were present, in some instances with evidence of organization.

DISCUSSION

These cases of varicella pneumonitis, like most of those recorded in the literature,[1-20] occurred in adults. Neonates and children may develop varicella pneumonitis, but its occurrence is uncommon.[4, 21, 22] Children with chickenpox are prone to secondary bacterial pneumonia.[2, 4] It is not known why adults have an increased susceptibility to the viral pneumonitis.

The incidence of varicella pneumonitis in adults is difficult to assess. In two small series, 30% of adults admitted to hospital with chickenpox developed pneumonitis.[3, 5] This figure may be high because only individuals with severe infections, and probably with complications, are likely to be admitted to hospital. The incidence of 16% found in 110 army personnel may be nearer the truth.[6] In that series all patients with chickenpox were admitted to hospital and all had a chest radiograph.

Sixty-nine per cent of the 148 cases of varicella pneumonitis reported in adults, including those detailed here, were males. The 18 cases in army personnel have been omitted.[6] Of the females, seven were pregnant:[5, 7, 14] one developed chickenpox in the first trimester, four in the second, and two in the third; five died. Fish[14] stated that there was no increased susceptibility to chickenpox during pregnancy. Mermelstein and Freireich[5] concluded that pregnant patients with varicella pneumonitis had a very poor prognosis. In our view, too few cases have been analyzed to accept firmly that males are more prone to the complication or that pregnant females with varicella pneumonitis have a poor prognosis.

The first patient recorded here presented in the classical manner. Respiratory symptoms usually develop when the skin eruption has been present two to five days. Often, as in Cases 3 and 4, the eruption is extensive, severe and sometimes hemorrhagic. A dry, initially non-productive cough is often the first sign (Cases 1 and 4); indeed, it may be the only one. However, in all but the mildest cases the cough is followed by dyspnea, tachypnea and cyanosis. In some cases the symptoms progress with frightening rapidity and severity (Cases 2 and 3). Physical signs in the lung are usually minimal during the first 24-48 hours but surprisingly marked changes may be seen in the chest film. In severe cases of pneumonitis, air entry is reduced and a few rales and expiratory rhonchi may be heard. It is unusual to have clinical evidence of pulmonary consolidation. Some patients, like the first and fourth in this series, develop pleuritic pain, but a pleural effusion is not a common complication. After 48 hours a little clear or mucoid sputum, sometimes streaked with blood, may be produced. Occasionally hemoptysis is severe.[4] As varicella pneumonitis is but one facet of a disseminated disease, patients may manifest lesions elsewhere. Vesicular lesions may be seen on the conjunctiva and mucous membrane of the mouth and pharynx (Cases 1 and 4) or, less commonly, the patients show evidence of myocarditis,[25] pericarditis,[16, 26] hepatitis,[4] pancreatitis (Case 3), orchitis,[27] or encephalitis (Case 3).

The course of the respiratory disease varies. If the pneumonitis is mild, cough may be the only symptom and may disappear within a week. In moderately severe cases (Case 1) the respiratory symptoms persist seven to 10 days. In severe cases (Case 2) death may ensue rapidly. Patients may die of other lesions caused by varicella, e.g. Case 3, in whom the opacities in the chest film cleared somewhat before she died; or they may die of complications, as did the patient (Case 4) who developed a massive secondary bacterial infection, perhaps related to his steroid therapy.

The radiographic signs of varicella pneumonitis[13, 15, 18, 24] are characteristic but not absolutely diagnostic, as other pulmonary diseases may induce identical changes. In mild cases they may be the only indication of a pneumonitis. In more severe cases they are always

more marked than are the corresponding clinical findings. Widespread bilateral nodular densities are seen superimposed on markedly increased bronchovascular markings. The infiltrates vary in size and are usually most marked in the hilar regions. The apices may be spared more than the rest of the lung, but no area is completely free. Some nodules are sharply defined; others merge with the surrounding lung substance. They may coalesce and give the appearance of consolidation, especially at the bases. Similar changes are caused by the viral pneumonitis which complicates herpes zoster infections.[28] However, this occurs far less commonly than varicella pneumonitis.

Laboratory tests reveal a normal or slightly raised leukocyte count with a polymorphonuclear leukocytosis. The markedly raised count in the third patient may have been due to her postpartum[36] state. The ESR is usually normal but may be elevated as in Cases 1 and 4. Throat and sputum culture reveals normal organisms. Cytological examination of sputum smears and sediments during the height of respiratory symptoms may show intranuclear inclusions in macrophages or bronchial epithelial cells.[29] Respiratory function tests carried out on 10 patients with varicella pneumonitis indicate that the ventilatory function is usually normal but that the alveolar capillary gas exchange is impaired.[23] Complement fixing antibodies may be demonstrated, and the virus may be isolated and grown in tissue culture.

The pathological changes found in the lungs in Cases 2 and 3 are similar to those described by others.[1, 12] The lungs are usually edematous and congested. An interstitial pneumonitis has a predominantly mononuclear cell infiltrate (Fig. 3). Hemorrhage, fibrin and occasional hyaline membranes are found in the alveoli. The alveolar walls may show focal necroses, sometimes related to small blood vessels. Septal cells may become cuboidal and form multinucleate giant cells, but the latter are not usually as numerous as in measles pneumonitis. Typical large acidophilic virus inclusion bodies are found in septal cells or macrophages.

The treatment of varicella pneumonitis is mainly supportive. In all cases except those with minimal clinical signs, an adequate supply of oxygen suitably humidified is the most significant factor. A wide-spectrum antibiotic is usually administered in the hope of preventing secondary bacterial infection, though Weinstein and Meade[2] in a small series of cases found that the course of the respiratory disease was not affected significantly by chlortetracycline. The

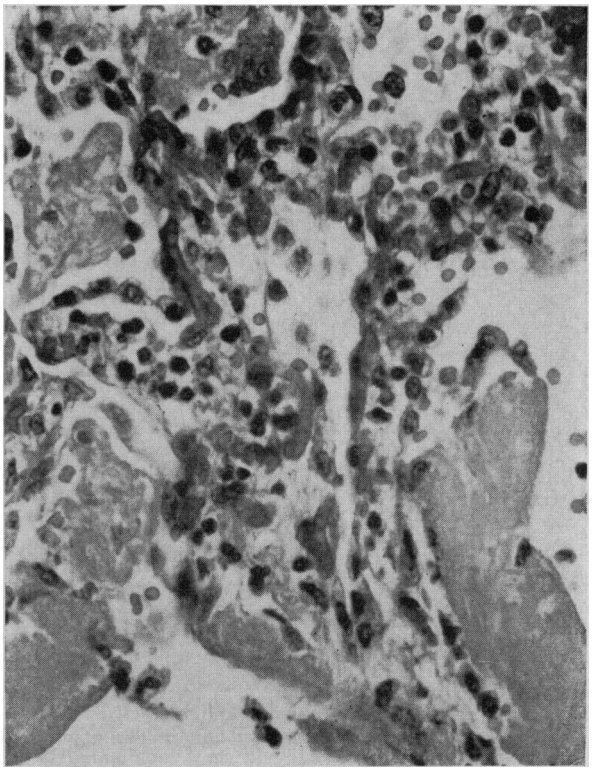

Fig. 3.—Interstitial pneumonitis with mononuclear inflammatory response (Case 3).

role for corticosteroids is still debatable.[30] Isolated reports of dramatic clinical improvement following corticosteroid therapy[4, 5] must be compared with reports of very severe cases often ending fatally, particularly in children receiving such treatment.[4, 31] It is not known whether corticosteroids caused the improvement or the deterioration. Krugman[4] and Mermelstein and Freireich[5] treated 44 adults successfully without administering steroids.

It is not certain that gamma globulin would protect adults from varicella pneumonitis. Ross[32] found in children that gamma globulin, given intramuscularly in a dosage based upon body weight and within three days of exposure, modified the clinical course. He did not favour its general use, preferring that it be given only to those subject to a special risk, e.g. children suffering from a blood dyscrasia or receiving antimetabolite or corticosteroid therapy. He pointed out that the action of gamma globulin administered to adults and pregnant women with no previous history of chickenpox might be of value, but made no specific recommendations on this point. Krugman[4] has stated that he favours its use in adults.

Patients with varicella pneumonitis may suffer residual pulmonary damage. There may be a

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prolonged period of breathlessness following the pneumonitis, or a defect in the alveolar capillary gas exchange may persist, often for several years.[23] Nodular opacities may be obvious in chest radiographs for weeks following clinical recovery, and then resolve, leaving a prominent reticular pattern which may last for months[9, 33] or longer.[24] Carstairs and Emond[20] suggested that the clearance of nodular shadows might be due to the absorption of fluid surrounding pulmonary lesions and that persistence of reticular markings might be caused by minute areas of necrosis scattered through the lung. Several authors are of the opinion that focal pulmonary calcification may be the end result of this process.[24, 33, 34] We favour the view of Abrahams *et al.*,[35] who state that a causal relationship between adult varicella pneumonitis and the subsequent development of pulmonary calcification, although not proved, is probable.

SUMMARY

Four cases of varicella pneumonitis in adults are presented. One male had mild respiratory symptoms and recovered. Two females, one pregnant, had severe symptoms and died. A second male died of a secondary bacterial pneumonia after presenting with symptoms of varicella pneumonitis. The clinical presentation and treatment are discussed. The lesions are described and mention is made of residual pulmonary changes.

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