such a disorder—the leuco-erythroblastic blood picture and histological evidence of haemopoiesis in the spleen, but the histological appearances of the bone marrow and biopsies were not those of myelofibrosis. The amount of bone marrow was excessive in both patients, despite extensive metastases in one of them (Case 1) and the absence of haemolysis or bleeding suggests that this cell proliferation was due to something other than simple compensatory hyperplasia. The monocytosis, present in both patients, could be a further manifestation of an abnormal marrow proliferation for, although blood monocyte counts are higher on average in patients with cancer, they rarely reach the level that was recorded in the first case (Barrett, 1970), and a monocytosis has been described in other myeloproliferative states (Maldonado and Hanlon, 1965).

Thus fibrosis of the bone marrow is not an essential feature of the myeloproliferative disturbance that has previously been described in patients with metastatic cancer. Furthermore, the failure to find tumour in the marrow of one of the present patients (Case 2) suggests that bone secondaries are not essential either. One explanation for this type of haematological complication of malignancy and of the myeloid metaplasia that has been described by others, is that some tumours elaborate a factor which stimulates fibroblastic, myeloid or erythroid

activity to a varying degree and also interferes with the control of cell release from the bone marrow. This would not be surprising with an oat cell carcinoma whose capacity for synthesizing various polypeptides with physiological properties is well known. In addition this would support the suggestion that marrow fibrosis is not the initial event in the pathogenesis of agnogenic myeloid metaplasia.

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Papilloedema associated with respiratory failure

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Summary

A case of papilloedema secondary to respiratory failure is reported which caused considerable diagnostic difficulty and led to extensive neurological investigation. Neurological complaints of headache and visual impairment overshadowed respiratory symptoms and were associated with gross haemorrhagic papilloedema. The case is compared with previous reports and the pathogenesis of papilloedema in respiratory failure is reviewed briefly. The similarity between the pathogenesis of this condition and benign intracranial hypertension is discussed.

Case history

A 49-year-old housewife presented in January 1976 with a 4-year history of progressively severe right frontal headache exacerbated by coughing and lying down and which was frequently worse in the mornings. For 6 months vision had been indistinct, with difficulty in reading newsprint, and one momentary episode of absolute visual failure had occurred during December 1975. The patient's general health was good apart from long standing chest symptoms of wheezing and dyspnoea on hills and stairs, which she attributed to a chest deformity

dating from childhood. She had smoked regularly fifteen cigarettes per day for 30 years and had recently taken salbutamol 4 mg t.d.s.

On examination she was a moderately obese alert lady, able to give a good account of herself. She had a dorso-cervical scoliosis, a short neck and low hairline. The cardiovascular system was normal, pulse 80/min, sinus rhythm with a blood pressure of 18.6/10.6 kPa. In the chest there were scattered inspiratory and expiratory rhonchi with some coarse bilateral basal crepitations. The most impressive clinical sign was bilateral high grade papilloedema with flame shaped haemorrhages. Corrected visual acuity was RIGHT 6/9 and LEFT 6/6. The only other abnormal findings were some impairment of alternate motion rate in the fingers and finger/nose ataxia on the left, together with heel/toe ataxia and a tendency to stumble to the left.

Investigations

Hb 15.2 g/dl; PCV 47.1; red cell indices and white blood cells were normal. Blood urea, electrolytes, calcium and phosphate, normal. Arterial blood gases: pH 7.34, PCO_2 6.5 kPa, PO_2 5.9 kPa, HCO_3 24.5 mmol/l. Chest X-ray showed multiple congenital abnormalities of the rib cage especially in the right upper zone, and a high dorso-cervical scoliosis convex to the right. There was cardiomegaly with some congestive changes in both lung fields. Only six vertebrae demonstrated in the cervical spine, and there was well marked disc degeneration at C5/6. Skull X-rays showed a minor degree of basilar invagination in a globular skull, hypotelorism but no evidence of raised pressure. The visual fields showed bilateral enlarged blind spots. The ECG showed pulmonale, right axis deviation and early right ventricular hypertrophy. The EEG revealed

only non-specific intermittent bilateral excess of theta activity. The gamma cerebral scan was normal.

Shortly after admission to hospital, the patient developed bilateral pitting ankle oedema without other evidence of congestive failure. Chlorthalidone 50 mg was added to her maintenance salbutamol. In view of the essentially negative findings, but persisting headache, pneumoventriculography was attempted via biparietal burr holes. This demonstrated a tense brain, but an attempt to cannulate the ventricles failed. Therefore, pneumoencephalography via the lumbar route was attempted, but after premedication with 10 mg papaveretum, the patient developed marked cyanosis and became very drowsy. Treatment with nalorphine, oxygen, doxapram, physiotherapy and later ampicillin and cloxacillin produced a gradual improvement in her respiratory state, although a temporary relapse occurred 4 days later. Serial arterial blood gas determinations are listed in Table 1. During this period, despite preservation of visual acuity, there was a marked deterioration in the fundal appearances with the development of bilateral subhyaloid haemorrhages (Fig. 1). Subsequently, lumbar pneumoencephalography showed small lateral ventricles (Fig. 2), centrally sited about the midline, a normal fourth ventricle and no evidence of a space-taking lesion or cerebellar ectopia. The CSF was normal, the protein being 0.11 g/l.

Progress

Dexamethasone 2 mg q.d.s. was commenced and intermittent 24% oxygen continued. The headache improved but at the time of discharge and again at review 6 weeks later there had been no appreciable change in the fundal appearances. Treatment at the time of discharge consisted of bendrofluazide

TABLE 1. Blood gases

Date	pH	PCO_2 (kPa)	PO_2 (kPa)	HCO_3 (mmol/l)
10.2.76	7.34	6.5	5.9	24.5
11.2.76				
(after papaveretum)	7.27	6.9	5.6	21.5
11.2.76				
(after 24% O_2)	7.34	8.6	6.3	30.0
12.2.76	7.49	7.3	7.4	39.0
13.2.76	7.46	6.3	8.0	32.0
15.2.76				
(no O_2 for 7 hr)	7.43	8.6	7.3	38.5
16.2.76				
(after 24% O_2)	7.46	6.3	8.0	32.0
20.2.76*				
(after 28% O_2)	7.42	6.4	—	30.0
24.2.76*				
(off O_2)	7.44	4.3	—	23.5
5.3.76	7.49	5.3	8.4	31.5
10.8.76	7.40	5.3	8.0	24.5

* PO_2 values were unreliable and are therefore omitted.

FIG. 1(a) and (b). Optic fundi showing bilateral high grade papilloedema and a triangular subhyaloid haemorrhage on the left.

FIG. 2. Lumbar air encephalogram: Townes' view with small lateral ventricles symmetrically sited about the midline.

10 mg daily with potassium supplements, salbutamol, prethcamide and dexamethasone 2 mg t.d.s. The steroids were gradually withdrawn over a 2-week period.

Three months after discharge the patient no longer complained of headache and commented that exercise tolerance had improved significantly following abstinence from cigarettes. On examination, the papilloedema had completely subsided with only a small triangular haemorrhage remaining in the infero-temporal quadrant of the left fundus. An EEG performed at this stage and a subsequent brain scan were normal.

Full lung function tests (Table 2) in April 1976 and February 1977 showed a severe restrictive and an obstructive defect. These are consistent with the patient's scoliosis and long term cigarette consumption.

Discussion

A patient with a long standing thoracic cage deformity and respiratory symptoms probably also associated with cigarette smoking, presented with progressively severe headache and high grade papilloedema. After investigations for an intracranial space-occupying lesion proved negative it was felt that the underlying cause was respiratory insufficiency. The duration of this was uncertain but it is known that carbon dioxide retention, hypoxia and respiratory failure can develop suddenly in patients with scoliosis and a rib cage deformity in their fourth and fifth decades (Godfrey, 1970). A gradual resolution of the neurological symptoms and signs followed an improvement in cardiopulmonary function although at follow-up there was a persistent abnormality of the arterial blood gases.

The association between papilloedema and respiratory failure was first described in 1933 by Cameron and subsequently other reports appeared in the literature (Meadows, 1947; Simpson, 1948; Westlake

and Kaye, 1954; Westlake, Simpson and Kaye, 1955; Sieker and Hickam, 1956; Conn *et al.*, 1957). In many of these reported cases, respiratory symptoms were prominent and neurological symptoms supervened later with the development of headache, mental confusion, tremor, twitching and altered consciousness. The appearance of papilloedema was often associated with gross hypercapnia and arterial P_{CO_2} levels of 12 kPa or more. This contrasts with the present patient who was fully alert and orientated on admission and in whom the respiratory symptoms were relatively unobtrusive, her arterial P_{CO_2} never exceeding 8.7 kPa. In their discussion of the neurological manifestations of chronic pulmonary insufficiency, Austen, Carmichael and Adams (1957) referred to their experience of patients in whom the neurological symptoms dominated the clinical picture so completely that the significance of respiratory features was overlooked or underestimated, and commented that diagnostic difficulty might arise under these circumstances. Although textbooks commonly cite respiratory failure and carbon dioxide retention as a cause of papilloedema, the fundal abnormalities are often less florid than those illustrated here and it may not always be appreciated that such severe changes can occur.

Hypercapnia, hypoxia, increased venous pressure and secondary polycythaemia have been implicated in the pathogenesis of the papilloedema of respiratory insufficiency. This patient certainly had hypercapnia and hypoxia and, although her venous pressure was not elevated clinically, there was radiological evidence of pulmonary congestion and she developed pitting ankle oedema. It is well known that hypercapnia stimulates cerebral vasodilatation resulting in increased cerebral blood flow and raised cerebral venous pressure (Kety and Schmidt, 1948). These in turn cause an elevation of cerebrospinal fluid (CSF) pressure (Simpson, 1954). The work of Patterson *et al.* (1955) demonstrated that the thresh-

TABLE 2. Lung function tests

	Predicted	Patient 2.4.76	% predicted	Patient 10.2.77	% predicted
Peak expiratory flow rate (l/min)	347	150	43	100	29
Forced expiratory volume in 1 sec (FEV ₁) (l)	2.05	0.95	46	0.95	46*
Forced vital capacity (FVC) (l)	2.40	1.45	60	1.25	52*
FEV ₁ /FVC%	87	66		76	
Residual volume (l)	1.40	0.92	66	1.22	87
Total lung capacity (l)	3.95	2.37	60	2.43	62
Transfer factor for carbon monoxide (ml/min/Torr)	22	13.3	60	14.7	67

* no change after bronchodilators.

hold for a cerebral vasodilator effect was an increase in arterial carbon dioxide tension of 0.55 kPa; therefore, potentially significant changes could occur with the degree of hypercapnia observed by the authors, without requiring the grossly elevated levels seen in some of the previously reported patients who developed papilloedema secondary to respiratory failure. Hypoxia also causes cerebral vasodilatation (Heyman, Patterson and Whatley Duke, 1952) and may be more important than hypercapnia in producing engorgement of the retinal vessels (Sieker and Hickam, 1956). The fundal appearances of the present patient on admission could have resulted from severe local congestion of the retinal veins or from raised intracranial pressure. Evidence of raised intracranial pressure was demonstrated at ventriculography and it appears that this was produced by a combination of hypercapnia and hypoxia. A striking deterioration of the fundal appearances with the development of subhyaloid haemorrhages followed the episode of acute respiratory failure precipitated by papaveretum. This may parallel the situation in high altitude climbers in whom hypoxia causes retinal vasodilatation making the retinal vessels vulnerable to a sudden rise in retinal venous pressure. Pre-retinal bleeding may then follow (Rennie and Morrissey, 1975; Shults, and Swan, 1975; Wiedman, 1975). Frank congestive cardiac failure has been prominent in cases in the literature and appears to contribute to the development of papilloedema. Although increased venous pressure *per se*, e.g. secondary to superior vena caval obstruction, need not produce raised intracranial pressure (Ferris, 1939; Hinshaw and Rutledge, 1942), pulmonary congestion may cause a critical enhancement of blood gas abnormalities so that papilloedema results. Resolution of the papilloedema in this patient was protracted after her cardiopulmonary status improved but as Leggat (1958) pointed out it may persist for some time after hypercapnia and raised CSF pressure have disappeared.

A recent study has shown an increased regional cerebral blood volume in benign intracranial hypertension although regional cerebral blood flow was marginally reduced (Mathew, Meyer and Ott, 1975). These authors suggest that venous engorgement and increased intracranial blood volume are important in the pathophysiology of the raised intracranial pressure in benign intracranial hypertension. The patient described in this report had cerebral vasodilatation and, presumably, increased cerebral blood flow, although there are no measurements of this or of intracranial blood volume. The ventricles at air encephalography were relatively small and their size was disproportionately less than might have been anticipated in a subject of her age with the

amount of air seen over the convexity of the cerebral cortex. The radiological appearances confirmed that the reason for the surprising previous failure to cannulate the ventricles in the presence of raised intracranial pressure was their size. This is of interest as the situation resembles that seen in benign intracranial hypertension. Cerebrovascular engorgement following obstruction of major dural sinuses, both internal jugular veins or the superior vena cava in association with benign intracranial hypertension has been documented (Bradshaw, 1956; Greer, 1962). The findings in the present patient provide additional support for the idea that disorders of cerebral vascular dilatation play a significant role in the pathogenesis of benign intracranial hypertension, although the primary aetiology may vary in individual cases.

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Miliary tuberculosis and disseminated aspergillosis

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Summary

A patient with concurrent miliary tuberculosis and disseminated aspergillosis is described.

Introduction

An association between *Aspergillus* infection and tuberculosis has long been recognized (Virchow, 1856; Lapham, 1926). *Aspergillus* is generally considered a harmless secondary saprophyte. A patient is described who developed concurrent miliary tuberculosis and disseminated aspergillosis, and whose clinical features suggested that both infections contributed to his illness.

Case report

A 42-year-old labourer presented with an 11-day history of an influenza-like illness. Six months and 1 month previously he had suffered two similar but milder episodes of illness, from which he recovered spontaneously. Otherwise he had been physically fit. On examination he was pale and ill. He had a temperature of 38°C, a membranous tonsillitis and a palpable liver and spleen (both one inch below the costal margin).

Initial investigations showed haemoglobin 11 g/dl; leucocyte count 1.7×10^9 /l; neutrophils 7%; lymphocytes 90%; monocytes 2%; platelet count 70×10^9 ; serum albumin 34 g/l; globulin 29 g/l; bilirubin 9 μ mol/l (0.5 mg/dl); aspartate transaminase 45 i.u./l; alkaline phosphatase 119 i.u./l (17 KAu.); IgG 7.8 g/l; IgA 2.1 g/l; IgM 1.0 g/l. Bone marrow aspirate was hypocellular. Blood, CSF, urine and throat swab were sterile. Tuberculin

test (1 : 10 000), Australia antigen, WR and Paul-Bunnell were negative. Chest X-ray was normal.

After obtaining cultures of blood, urine and faeces, he was treated with gentamycin and flucloxacillin without benefit. On the fourth day, after a lumbar puncture, he started treatment with streptomycin, isoniazid and ethambutol. Forty-eight hours later his temperature fell to normal, but after a further 48 hours he again developed a remittent pyrexia. During the next 10 days his condition deteriorated. Serum albumin fell to 26 g/l, alkaline phosphatase rose to 258 i.u./l (36 KAu.) and aspartate transaminase rose to 67 i.u./l. After a total of 13 days' treatment he developed a skin rash and antituberculous therapy was stopped. A trephine biopsy of the iliac crest showed reduced haemopoietic cells with increased lymphocytes, suggesting the possibility of lymphosarcoma. On the twenty-eighth day, exploratory laparotomy revealed small nodules up to 0.8 cm in diameter in the liver and spleen. Liver biopsy, lymph node biopsy and splenectomy were performed.

Following the histology report he started amphotericin intravenously and ethambutol, isoniazid and rifampicin orally. At the same time the original specimen of bone marrow grew acid-fast bacilli. Although his temperature started to settle, he remained desperately ill and died suddenly 5 days later.

Biopsy and post-mortem findings

Histology of the liver and spleen showed granulomas consisting of round collections of histiocytes