

ANSWER

From the question on page 1082

The lung biopsy showed a picture consistent with a congenital surfactant deficiency (either of protein B or C) or the absence of lamellar bodies in alveolar type 2 cells (fig 1).

Genetic analysis showed a de novo mutation in SFTP-C gene (I73T aminoacidic substitution). Diagnosis of surfactant protein C deficiency (SP-C) was formulated.

Hydroxychloroquine 10 mg/kg/day was started in the first twin, preceded by 3 months of prednisone 2 mg/kg/day because of the severity of the disease. As they began treatment, only one episode of upper airway infection occurred. After 18 months of continuous hydroxychloroquine treatment the respiratory rate at rest was 36/min and 34/min, respectively, and oxygen saturation 99%. The levels of physical activity were normal for age, digital clubbing was no longer evident and height raised back to 25th centile.

Surfactant protein C deficiency

Mutations in SFTP-C gene cause certain forms of interstitial lung disease which present both as recurrent lung infection and chronic hypoxaemia, cyanosis, clubbing and growth failure.¹ Moreover, I73T mutation is associated with an interfamilial phenotypic variability. Surfactant C seems to play an important role as a hydrophobic protein in stabilisation of surfactant. In heterozygous mutations the aberrant protein interacts with the regular pathway of regular SP-C biosynthesis, leading to inhibition of functionally active SP-C production. Lung damage is therefore induced both by SP-C deficiency in the alveolus and by aberrant proSP-C that cannot be handled by the protein degradation pathway and induces cellular injury and pulmonary inflammation.

In these patients hydroxychloroquine treatment seemed effective. Since prednisone was also used in one of the twins, a possible benefit from the combination of the two drugs can also be suggested. A worsening of the clinical condition after interruption of treatment would be needed to firmly confirm efficacy, even though the long lasting clinical improvement was remarkable.

The exact mechanism of action of hydroxychloroquine is unknown. Antimalarial agents have profound effects on macrophages by interfering with antigen presentation, by inhibiting production of inflammatory mediators such as interleukin (IL)1 and IL6 and by inhibiting activation of toll-like receptors. In SP-C deficiency the drug may act not only through an anti-inflammatory action but also by blocking the intracellular processing of SP-C precursors.² To our knowledge, only very few cases of SP-C deficiency successfully treated with hydroxychloroquine have been reported.^{3 4}

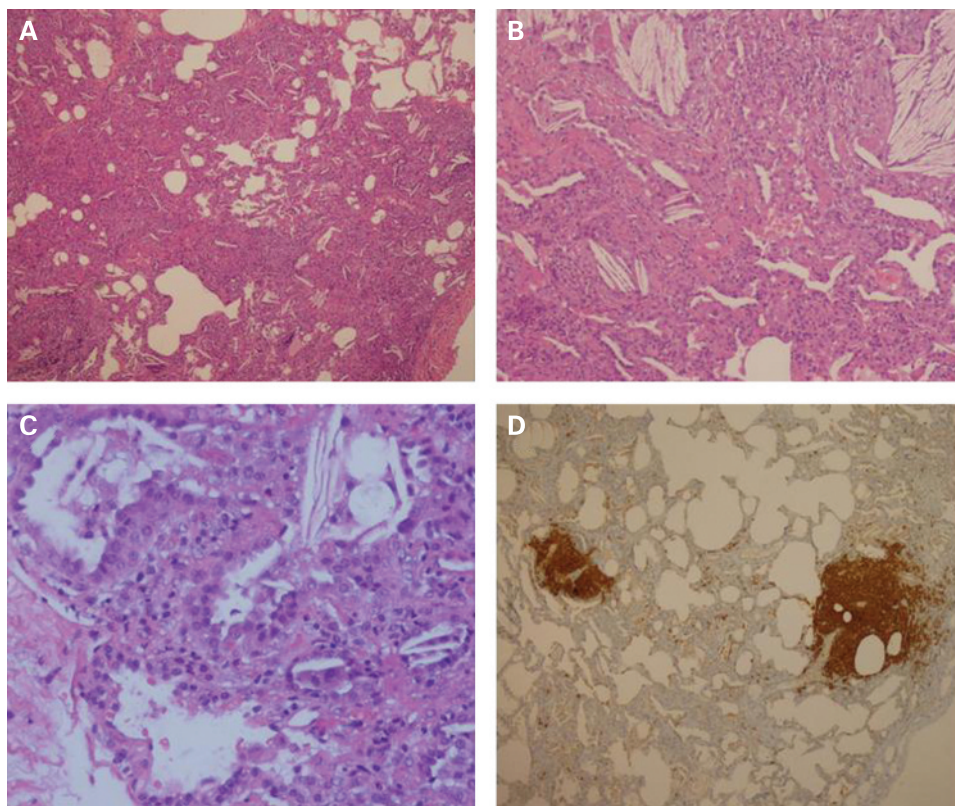
SP-C deficiency should be suspected in any case of unusually severe recurrent lung infections or undiagnosed interstitial lung disease in infants.

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Figure 1 (A) Open lung biopsy showing diffuse hypercellularity of alveolar walls and airspaces with focal overdistension due to disventilation. (B) Severe alveolar septal widening by chronic inflammatory cell infiltration (lymphocytes and histiocytes) without significant fibrosis. The airspaces show an increase in alveolar macrophages with diffuse phagocytosis of cholesterol clefts (endogenous lipidic alveolitis). (C) Focal PN2 cuboidal metaplastic changes with airspace consolidation by clustered alveolar macrophages (DIP-like pattern of macrophagic alveolitis). (D) BAL hyperplasia with predominant B lymphocytes CD20 positive.



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Pulmonary puzzle

Twins with severe recurrent chest infections

CLINICAL PRESENTATION

Two homozygotic twins were delivered at 31 weeks of gestational age by caesarean section, with birth weight 1490 and 1710 g, respectively. The family history was unremarkable. Their mother received steroid prophylaxis for hyaline membrane disease. They showed no perinatal problems. By the age of 8 months both had recurrent spells of respiratory distress,

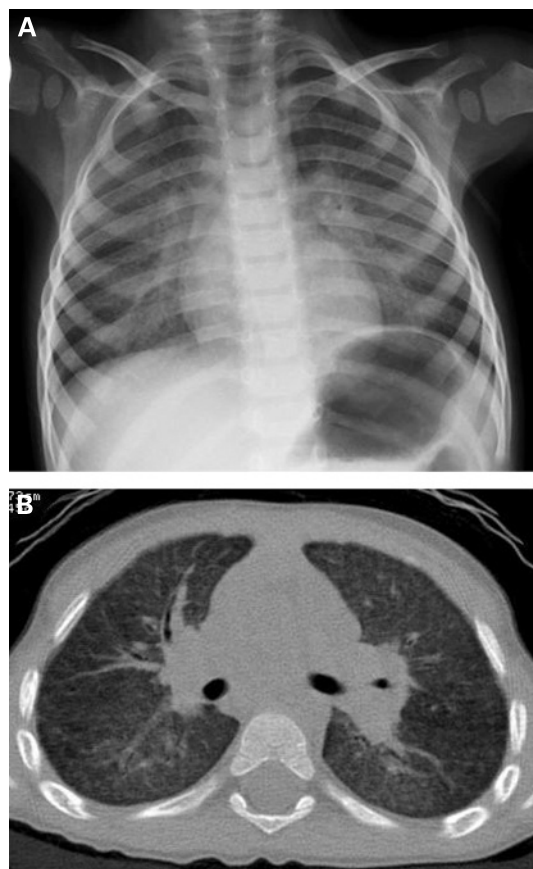


Figure 1 (A) Chest radiograph showing bilateral diffuse interstitial alveolar involvement. (B) High-resolution CT scan of the chest showing diffuse ground glass attenuation with interstitial pattern and fine nodules due to alveolar infiltrates throughout the lungs.

possibly triggered by viral infections, characterised by cough, fever, wheezing, tachypnoea, dyspnoea, desaturation, bilateral crackles and chest radiographs suggestive of an acute interstitial involvement. One twin had four admissions (two of these required orotracheal intubation) and the other had three (one with intubation). Each time they were empirically treated with oxygen, antibiotics, steroids and nebulised bronchodilators. Endotracheal tube suction cultures and tests for cytomegalovirus, *Pneumocystis* and *Mycoplasma* were negative.

By 11 months of age both showed progressive growth impairment (from 25th to 3rd centile) and, in the following months, reduced levels of physical activity. Physical examination progressively showed digital clubbing, chest deformities with flattening of the anteroposterior diameter, tachypnoea at rest (respiratory rate 60/min and 50/min) with oxygen saturation of 97% in both and no requirement for domiciliary oxygen.

Sweat tests, immunoglobulin levels, fecal elastase levels and lymphocyte subsets were normal. Genetic tests for cystic fibrosis, Schwachmann disease and mannose binding lectin deficiency were negative. The cardioechogram was normal with no evidence of pulmonary hypertension.

At the age of 30 months a chest radiograph performed in the twin with the most severe clinical history during a period of well being showed persistent findings of interstitial alveolar involvement (fig 1A). At that age his respiratory rate at rest was 60/min, heart rate 120/min, oxygen saturation 97% with digital clubbing. In the same twin a high-resolution CT scan of the chest revealed ground glass attenuation with interstitial pattern and fine nodules throughout the lungs (fig 1B).

QUESTION

What is your diagnosis?

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