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GOODPASTURE'S SYNDROME

Case Report with Emphasis on Pulmonary Physiology

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Introduction

Since the original description of Goodpasture's syndrome in 1919, extensive clinical and pathologic descriptions have been presented. Despite the obvious pulmonary involvement, few investigators have reported pulmonary physiologic data. This report is a presentation of a case of Goodpasture's syndrome in which pulmonary function studies were made.

Case Report

A 21-year-old student nurse was admitted to the Boston City Hospital with hemoptysis and dyspnea. She had been well until four months prior to admission when penicillin and later Dechlomycin® were given because of hemoptysis and fever; mild improvement ensued.

The patient's past history revealed an episode of proteinuria, and she had reacted positively to a Mantoux test, both when she was nine years old. At the ages of 10, 14, and 16 she experienced several episodes of pneumonia that were treated at home with antimicrobial drugs. She was free of pulmonary symptoms during the intervening years. At the age of 18 she had a normal intravenous pyelogram. There was no specific diagnosis or therapy reported. The patient denied cardiac disease and history of murmur, orthopnea, edema, allergy, and asthma. A grandfather had had tuberculosis and an aunt had had proteinuria but no pulmonary symptoms.

The patient denied any tendency toward bleeding, dermatologic symptoms, joint involvement, photosensitivity, gastrointestinal symptoms, relation of hemoptysis to menstrual cycles, or recent upper respiratory illness. She had donated several pints of blood previously. Physical examination was noncontributory.

For five weeks prior to the initial illness she was employed in a glass-manufacturing plant where exposure to volatile trichlorethane caused nasal and ocular irritation but no cough or hemoptysis.

On admission to the hospital the hematocrit was 29 per cent with hypochromic cells. The reticulocyte count was 0.1 per cent. The urine showed a trace of protein, and sputum yielded normal flora. Blood urea nitrogen was 21 mg per 100 ml. A chest film was interpreted as within normal limits but in retrospect revealed a fine nodular perihilar pattern. Bronchoscopy showed acute and chronic endobronchitis. Bleeding evaluation was normal, and numerous smears were negative for acid-fast bacilli. The hemoptysis subsided and she was discharged on iron therapy.

Progressive hemoptysis recurred, however, and exertional dyspnea became severe. Four weeks later the patient was readmitted to the hospital. She could walk only a few steps.

Physical examination revealed a well developed, thin, pale, white female with dyspnea on slight exertion. There was no chest pain and no expectoration of sputum other than frankly bloody material. The blood pressure was 125/60 mm Hg; pulse rate was 92 per minute; respiration, 16 breaths per minute, unlabored; and temperature was 99° F per os. Examination of the skin, joints, thyroid gland, and lymph nodes was normal. The conjunctiva were pale. Her chest was symmetrical with moderate excursions and fair breath sounds and clear to percussion and auscultation. The heart was not enlarged; the rhythm was regular and S_2P was greater than S_2A. An apical grade ⅙ systolic murmur was audible. Abdominal and neurologic examinations were normal. There was no cyanosis, clubbing, edema, or venous distention.

On this second admission the hematocrit was 23 per cent; the leukocyte count was 10,200 mm^3, with 78 per cent mature polymorphonuclear leukocytes, 16 per cent lymphocytes, 3 per cent monocytes, and 3 per cent eosinophils. Erythrocytes were hypochromic and microcytic. Reticulocyte count was 4.4 per cent. The platelets were adequate in number. The bone marrow showed marked erythroid hyperplasia (M:E ration 1:5). Serum iron was 11 μg per 100 ml. The half-time ^{51}Cr-labeled cells was 11 days (normal, 28 days). The initial blood urea nitrogen was 30 and rose to 59 mg per 100 ml in six days. Serum creatinine was 0.9 mg per 100 ml and rose to 7.5 mg per 100 ml ten days later. Fasting blood sugar was 82 mg per 100 ml, and plasma CO_2 content was 22.5 mEq per liter. The following serum values were determined: chloride, 109 mEq per liter; sodium,

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145 mEq per liter; potassium, 4.4 mEq per liter; calcium, 9.9 mg per 100 ml; phosphorus, 5.4 mg per 100 ml, total protein, 6.4 g per 100 ml with an albumin fraction of 3.6 g and a normal electrophoretic pattern; alkaline phosphatase, 1.8 Bodansky units; bilirubin, 1.3 mg per 100 ml; serum glutamic oxaloacetic transaminase, 18 units per ml; and prothrombin time, 13.0 seconds (control, 12.7 seconds). The urine was slightly cloudy with an acid reaction, specific gravity of 1.007, and contained red blood cells, hemoglobin, and waxy, granular, and red cell casts. Urine culture showed no growth of bacteria. The creatinine clearance was 87 ml per minute, and a total 24-hour urinary protein was 1.44 g. The antistreptolysin-0 titer was less than 100 units. C-reactive protein, latex fixation, and Coombs test were normal. Bleeding time was 2.5 minutes; clotting time, 7.5 minutes. Stool guaiac was negative. Sputum cultures yielded normal flora; two smears were negative for acid-fast bacilli. Iron stains of the sputum showed iron-laden macrophages. A tuberculin test with first strength PPD was negative. Chest films on admission revealed the presence of soft, confluent, mottled densities extending from both hilar areas consistent with an alveolar infiltration.

Clinical course: After admission the patient was given transfusions of whole blood until the hematocrit reached 28 to 30 per cent. An intravenous pyelogram was normal. A percutaneous right renal biopsy and lung biopsy were performed. Prednisone (up to 200 mg daily) and later Imuran® were given. The subsequent clinical course was gradually downhill as uremia progressed. Dialysis was not performed. The patient died 35 days after admission after a sudden episode of hemoptysis. The clinical course is summarized in figure 1.

Pathologic findings: Open lung biopsy revealed mild chronic bronchitis and focal hemosiderosis in macrophages (figure 2). There was no evidence of pulmonary hemosiderosis or Goodpasture's syndrome. The biopsy was taken from the lung periphery, which appeared grossly normal at thoracotomy and on roentgenographic examination.

Postmortem findings: Grossly, the significant findings were in the lungs and kidneys. The lungs weighed 1,700 g. In general, they were deep red in color and of firm consistency except for pink crepitant zones at the periphery of all lobes. Focal nodular bronchopneumonia was present in the right middle lobe. The trachea and major bronchi were filled with a frothy, bloody fluid extending into the tertiary radicles, and similar fluid oozed from the cut surface of the lung parenchyma. No focal bleeding point was found in the bronchi; the blood vessels were grossly normal. Separately the kidneys weighed 250 and 260 g. The capsule stripped easily revealing a smooth, diffusely "flea-bitten," cortical surface bilaterally. On cut section the cortex showed markedly congested pyramids with some fresh blood clots in one calyx.

Microscopic examination: The lungs (figures 3 and 4) showed large areas of intra-alveolar hemmorrhage, hemosiderin-laden macrophages, and focal acute bronchopneumonia. Alveolar septal rupture was found at the periphery with only little hemorrhage and a mild intra-alveolar edema. No other lesion of the alveolar septa was identified. Special stains such as, periodic acid-Schiff, (PAS), and periodic acid-Schiff with picric acid counterstains, luxol fast blue, van Gieson, and toluidine blue, failed to disclose any additional changes. No lesion of the pulmonary blood vessels was demonstrated by elastic tissue stains. Phosphotungstic acid-hematoxylin stain showed only occasional fibrin clumps enmeshing erythrocytes. In the kidneys most glomeruli showed profuse epithelial proliferation with crescent formation and deposits of dense eosinophilic (PAS positive) material in the tufts. Bowman's space contained erythrocytes and no polymorphonuclear leukocytes. The basement membrane of Bowman's capsule showed varying degrees of thickening but no distortion. No periglomerular fibrosis or interstitial inflammatory infiltrate was present. The tubules contained numerous erythrocytes, PAS-positive casts, and an occasional polymorphonuclear neutrophil.

Pulmonary Function Studies

Initial studies were performed prior to lung biopsy and therapy. Most studies were completed when the patient was anemic and moderately ill (table 1). Simple assessments of her mechanics of breathing and measurements of lung volumes indicated a restrictive process with no evidence of airway obstruction. There was significant abnormality in inert gas distribution. Hyperventilation with an increase in alveolar ventilation ($\dot{V}_A$), slightly increased alveolar oxygen tension ($P_{A_{O_2}}$) and reduced arterial carbon dioxide tension (Pa_{CO_2}) were present at rest and were associated with an increased oxygen consumption. The ratio of dead space to alveolar ventilation was low. The alveolar-arterial oxygen tension gradient (Aao_2D) was 60.7 mm Hg. The major defect was a significantly reduced carbon

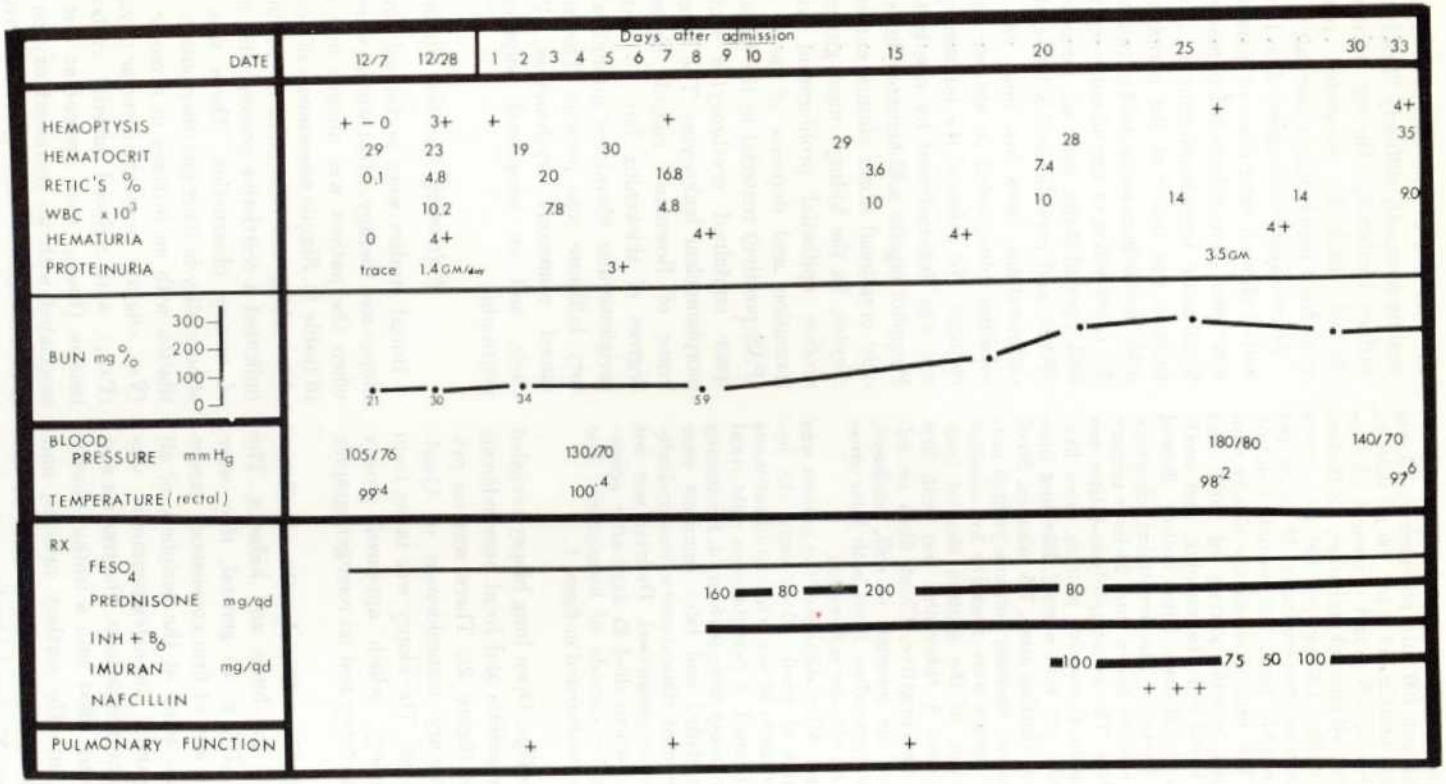

FIG. 1. Summary of clinical course.

monoxide diffusion capacity with an arterial oxyhemoglobin saturation that was low at rest and fell precipitously with exercise. The extent of venoarterial shunting that may have resulted from the alveolar septal and interstitial fibrosis was not evaluated. Some shuntlike process was suggested by the Pa_{O_2} of 483 mm Hg observed after the patient breathed 100 per cent oxygen for ten minutes; further oxygen breathing could not be tolerated.

Five days later after transfusion and a somewhat improved clinical state, the vital capacity (FVC) was 2.2 liters, and eight days later with the clinical situation fairly stable the vital capacity was 1.925 liters.

Discussion

This case fulfills the criteria currently considered essential to Goodpasture's syndrome: (*1*) initial hemoptysis and pulmonary infiltrate; (*2*) azotemia and iron deficiency anemia; (*3*) glomerulitis with progressive uremia; and (*4*) absence of gross arteritis (1). Of the approximate 105 reported cases, this is the eighteenth example in a female (2).

The fairly constant microscopic findings in the lungs of such patients include intra-alveolar hemorrhage, hemosiderin-laden macrophages, and fusiform thickening of the intra-alveolar septa with various degrees of collagenization (1). This patient had no appreciable thickening of intra-alveolar septa, and fibrosis was minimal or absent; however, it should be noted that the patient was on steroid therapy. Other microscopic abnormalities reported inconstantly include hemosiderin-laden macrophages within the septa, prominent alveolar lining cells, organized aggregates of fibrin within alveoli hyaline membranes, intraseptal leukocytes (3), and bronchopneumonia. Of these features, our patient showed only focal acute bronchopneumonia and minimal intra-alveolar fibrin. Disintegration, splitting, and partial dissolution of the alveolar capillary basement have been stressed as a point of morphologic differentiation from idiopathic pulmonary hemosiderosis (4). In this patient, rupture of the septa in peripheral areas was identified; however, special stains did not reveal the other previously mentioned changes. The fibrinous, proteinaceous, intra-alveolar exudate characteristic of uremia was absent. It is interesting that the open lung biopsy was essentially

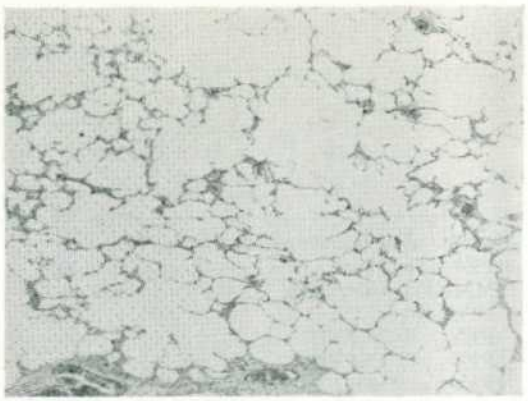

Fig. 2. Open lung biopsy specimen; (original magnification × 90).

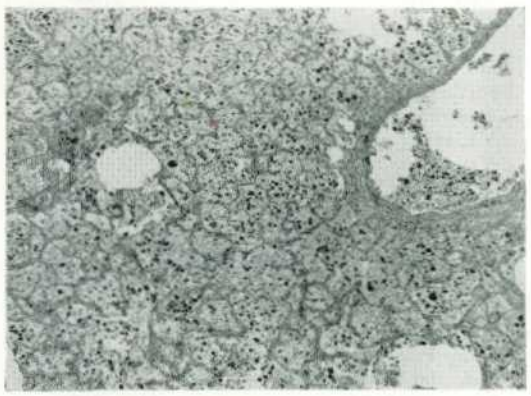

Fig. 3. Low-power view demonstrating intra-alveolar and intrabronchial hemorrhage; (periodic acid-Schiff stain; original magnification × 90).

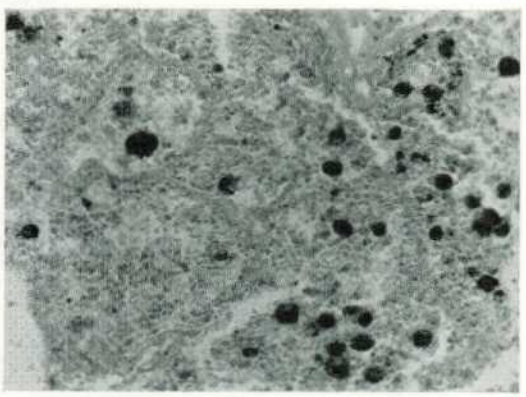

Fig. 4. Iron stain demonstrating erythrocytes and hemosiderin-laden macrophages; (original magnification × 400).

TABLE 1
PULMONARY FUNCTION DATA

Test	Date of Test: December 30 Predicted	December 30 Observed	December 30 βABD*	January 4	January 12
Mechanics of breathing, sitting					
PEFR, *liters/min*†	>300	385	385	385	365
MMEFR, *liters/min*	264 ± 48	109	99	100	98
FVC, *liters*	3.230	1.8 (56‡)	2.0 (62)	2.2 (68‡)	1.9 (59)
FEV_1, *% of FVC*	80	86	81	92	100
FEV_3, *% of FVC*	95	99	98	99	100
$FEV_{0.75} \times 40$, *liters/min*	94	55 (58‡)	57 (61‡)	80 (85‡)	75 (80‡)
Lung volumes, sitting, ml BTPS					
IC		1,244			
ERV		1,238			
VC	3,230	2,482 (76.5‡)			
FRC (He)	2,900	1,938			
RV	1,440	700 (49.0‡)			
TLC	5,320	3,182			
RV/TLC, %	<35	21			
Ventilation, supine					
Respiratory rate, *breaths/min*	18.0	18.0			
V_T, *ml*	550	496			
$\dot{V}_E$, *liters/min*	7.0	8.928			
V_D, *ml*	175.0	88.9			
V_D/V_T, %	<35	19.0			
$\dot{V}A$, *liters/min*	5.0	7.22			
Single breath O_2 test: N_2 distribution, %	<3.0	3.8			
Gas exchange, supine					
$P_{A_{O_2}}$, *mm Hg*	100–110	120.7			
$P_{A_{O_2}}$–Pa_{O_2}, *mm Hg*	10–15	60.7			
$\dot{V}_{O_2}$, *ml/min*	250	261			
$\dot{V}_{CO_2}$, *ml/min*	215	210			
R	0.8	0.8			
Dco (steady state), *ml/min/mm Hg*	24.5	4.6			

Test	At Rest	Exercise§	Ten Minutes of 100 Per Cent Oxygen
Blood gases, supine			
Pa_{O_2}, *mm Hg*	60	39	483
Pa_{CO_2}, *mm Hg*	24	22	23
pH	7.48	7.51	7.50
Sa_{O_2}, %	91.8	70.9	100
Hco_3, *mEq/liter*	17.8	17.2	17.2

Key: PEFR, peak expiratory flow rate; MMEFR, maximal midexpiratory flow rate; FVC, forced vital capacity; FEV_1, one-second forced expiratory volume; FEV_3, three-second forced expiratory volume. For other symbols see Fed. Proc., 1950, *9*, 602.

* After aerosol isoproterenol.

† Measured by Wright's peak flow meter.

‡ Numbers in parentheses denote percentages.

§ Forty-five watts Godart ergometer × six minutes.

normal at a time when the chest film revealed moderate involvement.

Limited pulmonary physiologic data are available in Goodpasture's syndrome and must be analyzed with due regard for complicating cardiac failure, uremia, anemia, and pulmonary infections. Bates and Christie (5) reported a case of Goodpasture's syndrome in a 20-year-old male

in whom there was parenchymal involvement and anemia of 7.6 g per 100 ml hemoglobin. The total lung capacity and vital capacity were reduced by 30 to 35 per cent, but ventilatory function was normal. The diffusing capacity at rest and during exercise was reduced to approximately 50 per cent of predicted. The exercise diffusing capacity remained abnormal despite an improved clinical course and clear chest film one month later. Ventilation was increased out of proportion to oxygen uptake.

In the cases reviewed by Benoit and associates (1), 3 patients with variable pulmonary involvement showed a normal vital capacity with normal and one- and three-second forced expiratory volumes. The maximal breathing capacity was 100 per cent of predicted with moderate disease. Two patients were reported to have oxygen saturations of 94 to 96 per cent. In one case the RV/TLC ratio fell from 30 to 18 per cent (1).

Randall and co-workers described a 35-year-old male with moderate pulmonary involvement, who was studied after blood transfusions (6). The vital capacity, total lung capacity, and residual volume were reduced to 70 per cent of predicted. There was no evidence of airway obstruction. Pulmonary diffusion capacity for carbon monoxide (method not specific) was just below the lower limit of normal. Arterial blood oxygen tension was 67 mm Hg; carbon dioxide tension was 24 mm Hg, pH 7.46; and oxygen saturation was 94 per cent.

The 16-year-old patient of McCall and associates (7) experienced a benign course. The hemoglobin was 11.5 g per 100 ml, and blood urea nitrogen was 22 mg per 100 ml. Pulmonary function studies performed when roentgenograms of the chest showed only small patchy densities in the right lung base revealed "normal ventilatory reserve with no airway obstruction, normal oxygen saturation at rest, during exercise, and after breathing 100 per cent oxygen, and a normal acid-base pattern." More specific data were not given.

In the present case, correlation of physiologic findings with observed pathologic findings is of interest. A restrictive ventilatory pattern and a significant diffusion defect were observed. The major factor responsible for arterial hypoxemia appeared to have been impaired diffusion, although venoarterial shunting and inhomogeneity of ventilation and perfusion were not entirely eliminated. Similar restrictive diseases with diffusion defects, e.g., pulmonary hemosiderosis (5), may be related to diffuse parenchymal fibrosis. Benoit and associates (1) stress the presence of thickened, collagenized alveolar septa, and intra-alveolar hemorrhage and hemosiderin macrophages in Goodpasture's syndrome. However, the pathologic material from our patient revealed minor thickening of alveolar septa and minimal fibrosis, perhaps because she had been on steroid therapy. The major anatomic features were focal bronchopneumonia, alveolar fibrin deposition, and widespread alveolar hemorrhages. The ventilatory restriction and reduced pulmonary diffusion of carbon monoxide were observed during a clinical period of toxicity and anemia (hematocrit 21 g per cent) and may be related to these factors, but more likely is related to the presence of intra-alveolar hemorrhages. Thus, the available data indicate that Goodpasture's syndrome is characterized physiologically by variable degrees of ventilatory restriction and a diffusion defect, which result from extensive intra-alveolar hemorrhage with or without significant degrees of interstitial fibrosis, depending upon the course of the disease.

Careful gross and microscopic examinations failed to reveal a specific lesion responsible for the intra-alveolar hemorrhages. Thus, the terminal gross hemoptysis is puzzling. From the histologic distribution, changes in the alveolar-capillary membrane, which may be limited to the basement membrane (8), appear to result from as yet ill-defined factors. The acute intra-alveolar "bleeding" causes death, in part, by asphyxiation. Fluorescent antibody studies have revealed gamma globulin on the renal glomerular basement membrane, suggesting that the altered lung contains an antigen that participates in the production of hyperimmune glomerulonephritis (9). There was no evidence that steroids or Imuran® were beneficial to this patient, but improvement has been observed in some cases (10). The cause of proteinuria at age 9 in our patient was never defined, and its relationship to the terminal events is not clear. Many patients with Goodpasture's syndrome have had a history of prior viral illness or exposure to a toxic substance (11). A potentially offending material in this case was trichlorethane, a volatile organic solvent used in the glass-manufacturing process. The role of other unidentified agents acting as

antigens or toxins following a latent phase is entirely speculative.

SUMMARY

The eighteenth case of Goodpasture's syndrome occurring in a 21-year-old girl is presented. The clinical and pathologic features of this case were similar to those reported by others except that pulmonary fibrosis was minimal. Pulmonary physiologic data revealed an advanced restrictive ventilatory process with a significant diffusion defect. These abnormalities appeared to be primarily related to massive intra-alveolar hemorrhage. The physiologic and pathologic data are discussed in the light of present knowledge of the disorder.

RESUMEN

El Síndrome de Goodpasture. Informe de Caso con Enfasis en la Fisiología Pulmonar

Se presenta el décimo octavo caso de síndrome de Goodpasture en una mujer de 21 años. Los hallazgos clínicos y patológicos de este caso son similares a los ya informados, excepto que la fibrosis pulmonar era mínima. Las pruebas funcionales pulmonares revelaron un proceso restrictivo respiratorio avanzado, conjuntamente con una importante deficiencia difusora. Esto respondía principalmente a hemorragias intra alveolares masivas. Se discuten los hallazgos fisiológicos y los patológicos, a la luz del actual conocimiento sobre la enfermedad.

RESUME

Syndrome de Goodpasture—Relation d'un cas, avec considération spéciale quant à la physiologie pulmonaire

On présente ici le dix-huitième cas de syndrome de Goodpasture, survenu chez une fille de 21 ans. Les caractéristiques cliniques et pathologiques de ce cas sont semblables à celles rapportées par d'autres auteurs, si ce n'est que la fibrose pulmonaire était ici minimale. Les données de la physiologie pulmonaire ont révélé un processus avancé de restriction de la ventilation, avec des troubles significatifs de la diffusion. Ceci s'est révélé être directement en rapport avec une hémorragie intra-alvéolaire massive. Les données physiologiques et pathologiques sont discutées à la lumière de nos connaissances actuelles dans le domaine de cette maladie.

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