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BRONCHIAL ASTHMA

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Definition

- Bronchial asthma (BA) – a chronic inflammatory disease of the airways involving eosinophils, lymphocytes (T helper cells), macrophages, basophils, mast cells, neutrophils, which is characterized by generalized bronchial obstruction of different severity, which may be partially or fully reversible (spontaneously or under bronchodilator effect), and the phenomenon of bronchial hyperreactivity. **(Global strategy for the prevention and treatment of asthma, GINA).**

The Global Initiative for Asthma; GINA

- This initiative was created with the aim of raising awareness of BA among medical professionals, health authorities and society in general to improve the prevention and treatment of BA by coordinating efforts around the world. GINA prepares scientific reports with BA, promotes the dissemination and implementation of recommendations, and also supports international cooperation in the field of BA research. The GINA 2016 preview and other GINA publications can be found at **www.ginasthma.com**

Etiology

- Chronic inflammation can be induced through contact with an allergen, pollutants, industrial factor, and acute viral infection. The inflammatory process leads to four forms of bronchial obstruction, acute spasm of smooth muscles of the respiratory tract, subacute swelling of the mucous membrane of the respiratory tract, chronic formation of viscous bronchial secretions and irreversible sclerotic process in the airways. BA may be of non-allergic origin, such as a brain injury, resulting in endocrine disorders. Infectious-allergic asthma develops against various infectious respiratory disease (pneumonia, bronchitis, tonsillitis, nasopharyngitis), where bacteria are antigens. In most cases, they are opportunistic and saprophytic flora (S. aureus, E. coli, Klebsiella spp.).

Causes

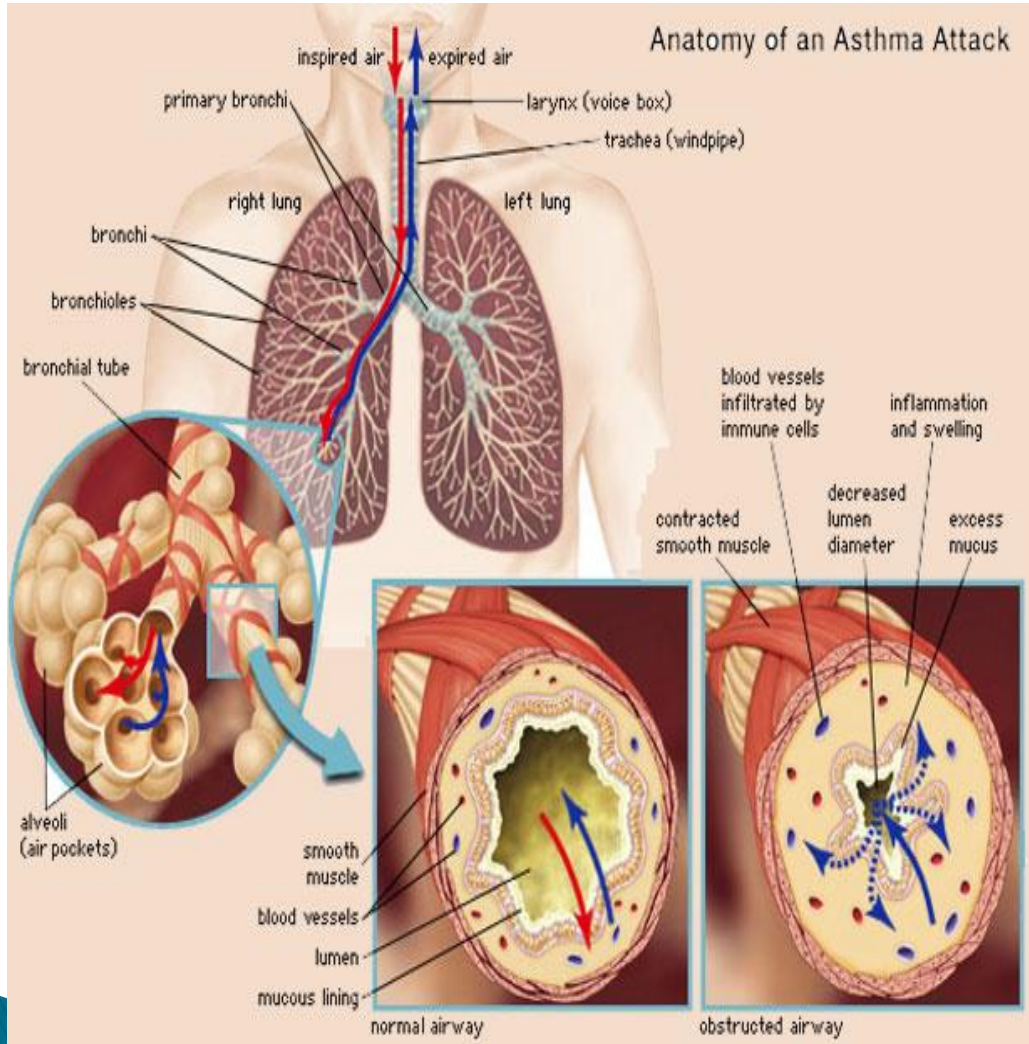
Inducers of asthma most often are:

- – Household allergens
- – Allergens of animal origin: wool, feathers, droppings, saliva of animals and insects, Daphnia and other;
- – Fungal allergens, mold and yeast fungi (Alternaria, Aspergillus, Mucor, Candida, Penicillum, Cladosporium);
- – Pollens allergens three main plants: trees, shrubs, grasses and weeds;
- – Food allergens;
- – Drugs: antibiotics, particularly penicillin, vitamins, aspirin and other nonsteroidal antiinflammatory drugs;
- – Viruses and vaccines

Pathogenesis

- The inflammation of the bronchial mucosa occurs at the early stages of asthma. Activation of T-helper cells leads to the production of cytokines that characterize as "allergic" inflammation. There is also a migration of eosinophils into the bronchial tree, their activation with subsequent release of vasoactive substances that damage the bronchial mucosa tissue. Neutrophil's inflammatory nature predominates in acute severe asthma attacks associated with sudden death. In severe forms of asthma there is increase in the number of macrophages. Mast cells play an important role in the immediate response to allergen exposure due to the production of proinflammatory cytokines. The consequence of chronic inflammation in asthma is remodeling of lung tissue, destruction of epithelial cells by desquamation thickening basement membrane disruption basic substance, hyperplasia and hypertrophy of smooth muscles of the bronchi. There is a relationship between the concentration of serum immunoglobulin E (IgE), the clinical signs of bronchial asthma and hyperreactivity.

- In the pathogenesis of asthma are three stages: 1) immune – under various allergens produce antibodies or lymphocytes sensitization occurs; 2) patochemical – with repeated action of allergens out of mast cells mediators; 3) pathophysiological – development of bronchial obstruction syndrome.


Anatomy of an Asthma Attack
inspired air
expired air
primary bronchi
larynx (voice box)
trachea (windpipe)
right lung
left lung
bronchi
bronchioles
bronchial tube
alveoli
(air pockets)
blood vessels
infiltrated by
immune cells
inflammation
and swelling
contracted
smooth muscle
decreased
lumen
diameter
excess
mucus
smooth
muscle
blood vessels
lumen
mucous lining
normal airway
obstructed airway

Classification of asthma

- According to this classification, the patient's condition is determined by the severity of asthma. Intermittent (episodic) course, persistent (permanent) course are: easy, moderate and hard.

Intermittent asthma

Clinical symptoms before treatment:

Symptoms (episodes of coughing, wheezing, shortness of breath) short-term, there are at least 1 time per week for at least 3 months

- Short-term aggravation
- Night symptoms occur no more than 2 times a month
- The absence of symptoms, normal values of between exacerbations.FEV1(Forced Expiratory Volume in one second) or Volume of exhale> 80% of the relevant
- Daily fluctuations Volume of exhale or FEV1<20%.

Easy persistent asthma

Clinical symptoms before treatment:

- • Symptoms often, at least – once day a week, but less than 1 time per day for more than 3 months
- • Exacerbation of symptoms can disrupt sleep and activity;
- • The presence of chronic symptoms that require symptomatic treatment almost daily;
- • Night asthma symptoms occurring more than 2 times a month;
- • FEV1 or Volume of exhale> 80% of the relevant
- • Daily fluctuations Volume of exhale or FEV1 – 20–30%.

Middle severity of persistent asthma

Clinical symptoms before treatment:

- • Symptoms occur daily
- • Worsening lead to disruption of activity and sleep
- • Night asthma symptoms occur more than 1 time per week
- • The need for daily intake β2-agonists short action
- • FEV1 or Volume of exhalewithin 60-80% of the relevant
- • Daily fluctuations Volume of exhaleor FEV1 > 30%.

Severe persistent asthma

Clinical symptoms before treatment:

- There is presence of largely variable long symptoms, frequent nocturnal symptoms, activity limitation, and severe exacerbation. Despite the treatment, which is carried out, the absence of proper control of the disease
- • The constant presence of long daytime symptoms;
- • Frequent night symptoms;
- • Frequent, severe exacerbation;
- • Limit physical activity caused by asthma;
- • FEV1 or Volume of exhale30%;

Clinical manifestations of asthma

Symptoms of asthma:

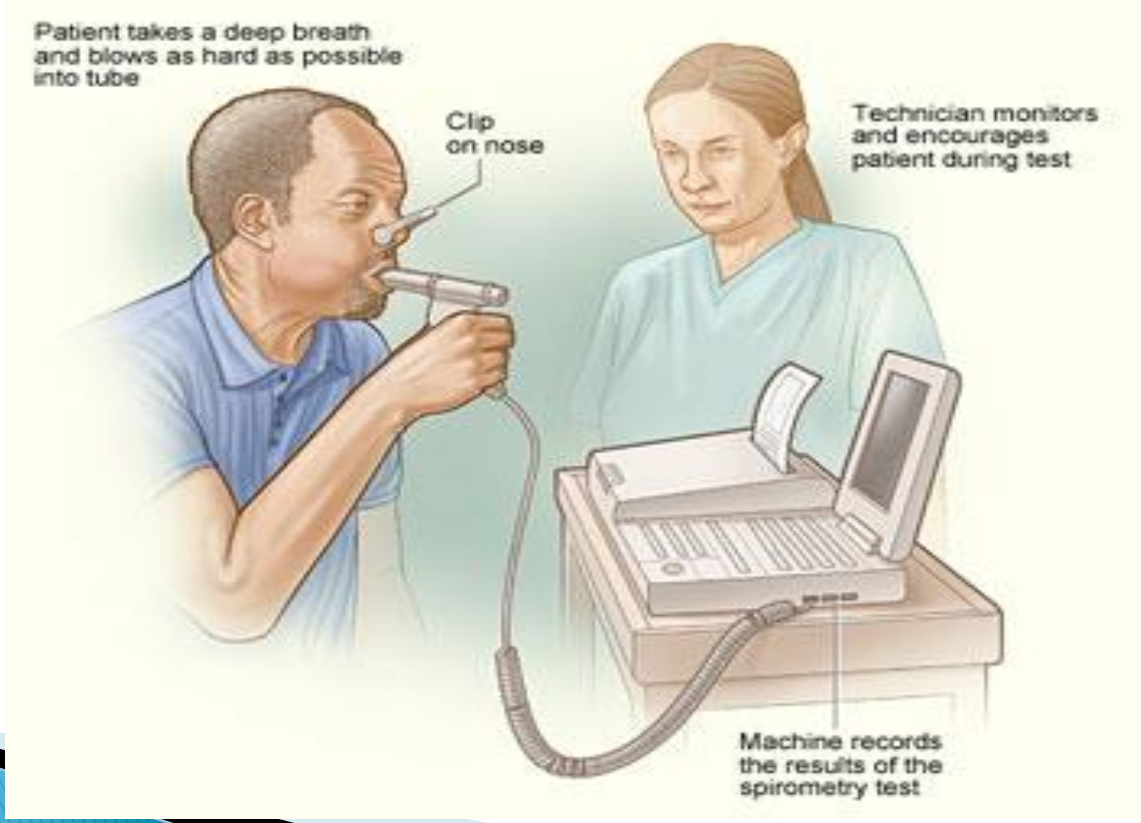
- – Episodic breathlessness with difficulty in exhaling;
- – Cough more at night and during exercise;
- – Occasional whistling wheezing in the lungs;
- – Stiffness of the chest.
- Symptoms are mostly aggravated at night and in the early morning hours, and awaken the patient

Examination

- During the attack patients often take a forced sitting or standing position with incline of body forward, leaning on hand with a raised shoulder and summary
- Severe emotional reaction – the patient concerned, suffering facial expression, scared, can barely speak.
- The face of the patient during an attack puffy, covered with cold sweat, wings swellsof nose during inhalation, neck veins dilated

«Gold standart» for diagnostics BA

- **Spirometry** is one type of pulmonary function test. Spirometry is a simple test to measure how much (volume) and how fast (flow) you can move air into and out of your lungs.



Additional laboratory and instrumental examination

- 1. Hemogramm (Eosinophilia, lymphocytosis, and a tendency to leukopenia. Prolonged severe course may develop compensatory increase of erythrocyte and hemoglobin).
- 2. Analysis of sputum (eosinophilia bronchial secretions, Curschmann's spirals, Charcot-Leyden crystals).
- 3. X-ray study (as determined by increased transparency of the lung fields, strengthening of pulmonary picture, the expansion of the roots of the lungs. The typical low standing, low mobility dome of diaphragm. The ribs are horizontally extended intercostal spaces).
- 4. Electrocardiography (increase in T wave in all leads, often increasing the P wave in leads II and III. In severe hypoxia infarction observed depression ST segment in I, aVL, V 4-6 leads.
- 5.Alergic study (Allergic history - the presence of allergic rhinitis patients, atonic dermatitis or asthma or atonic disease in his family, Leather positive tests with allergens, elevated levels of total and specific IgE).

Treatment of asthma

- Drug therapy for asthma patients spend using different routes of administration of drugs – inhaled, oral and parenteral. The greatest advantage is inhalation, providing a strong local effect of drugs in the lungs without causing their unwanted systemic effects, makes it possible to accelerate the positive effect of treatment due to lower doses of medication.

- Used daily basis, the long-term basis, to achieve and maintain control of persistent asthma. Include inhaled corticosteroids, systemic corticosteroids, cromones, leukotrienes modifiers, longacting bronchodilators (inhaled β2-agonists, long-acting oral β2-agonists, long-acting, longacting theophylline, long-acting anticholinergs) and systemic Steroid-Sparing therapy

- Medications are usually given as a metered dose inhalation:
- – spacers
- – pocket powder inhalers (spinhaler, turbohaler, rotohaler)
- – ultrasonic inhalers
- – compressor nebulizer inhalers
- Nebulizers and spacers are equally effective in those with mild to moderate symptoms.

A Case of Asthma 1

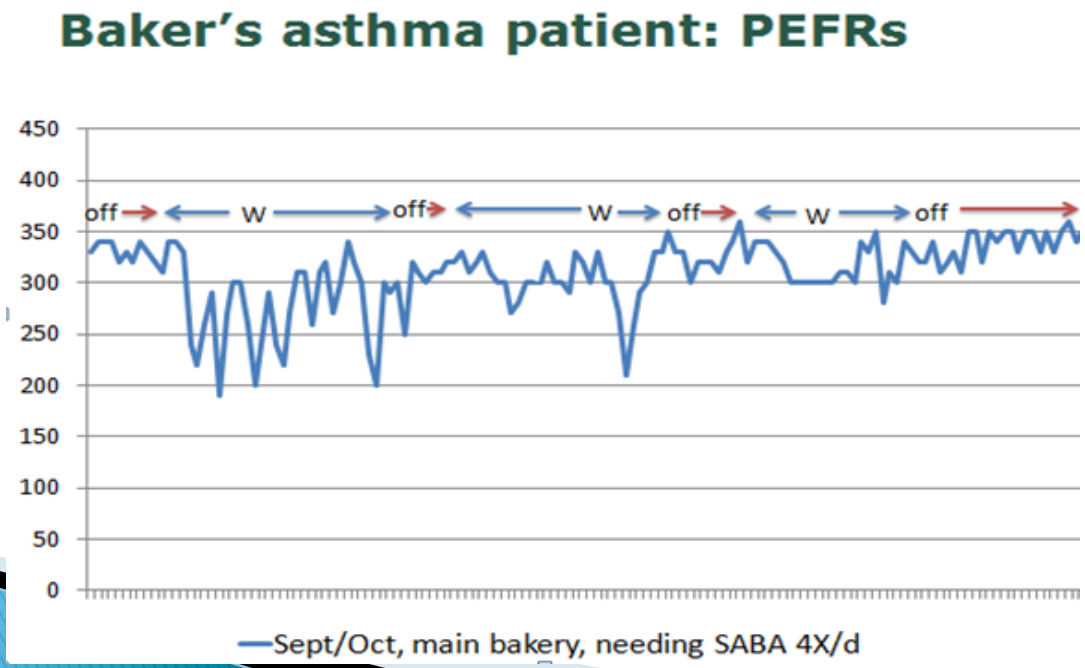
- A 44 year old woman, currently working in a bakery, presents with a 1 year history of asthma and allergic rhinitis symptoms, including episodic cough, wheeze, shortness of breath and chest tightness with itchy red watery eyes and a stuffy, runny, itchy nose. These symptoms become worse within 1-2 hours of starting work each day, and worsen throughout the work week. She especially finds red bran to worsen her symptoms almost immediately on exposure. She notices an improvement within 1-2 hours outside of being at her workplace. She has been working in the bakery for 13 years, and for the last 10 years has been a "pre-scaler", weighing components, while wearing a paper mask. The line that she has worked on for the last 2 years is dustier than other areas.
- Her past medical history is significant for seasonal allergic rhinitis in the summer months since childhood. She is a lifelong non-smoker. Her family history is significant for asthma in her mother and brother. She currently uses an inhaled steroid-long acting bronchodilator (ICS-LABA) daily, and inhaled short-acting bronchodilator (SABA) as needed, generally up to 4 times a day at work with relief.

Physical Exam

- Her physical examination is normal.

Lab

- Her chest x-ray is also normal. Spirometry testing shows FEV1/FVC 0.62 (within 24 hours of work), FEV1 1.9L (60% predicted), and post-bronchodilator, the FEV1 increases to 2.2L (300cc, 16%). One year earlier, after 2 months off work, her FEV1 was 2.3L. Skin prick testing was positive to grass (3+), a slurry of workplace flour (3+), wheat germ (3+), and red bran (2+). Her home peak expiratory flow readings ranged between 270 and 340, with lower readings on workdays



Diagnosis and Management

- A diagnosis of occupational asthma from wheat (including wheat germ and bran) was made. She was transferred to a muffin packing area where flour exposure was minimal, if any, and was followed with further peak flow monitoring and spirometry: she has since remained well with no symptoms and requiring no medications.
- Spirometry testing shows FEV1/FVC 0.62 (within 24 hours of work), FEV1 1.9L (60% predicted), and post-bronchodilator, the FEV1 increases to 2.2L (300cc, 16%). One year earlier, after 2 months off work, her FEV1 was 2.3L. Skin prick testing was positive to grass (3+), a slurry of workplace flour (3+), wheat germ (3+), and red bran (2+). Her home peak expiratory flow readings ranged between 270 and 340, with lower readings on workdays

Question 1

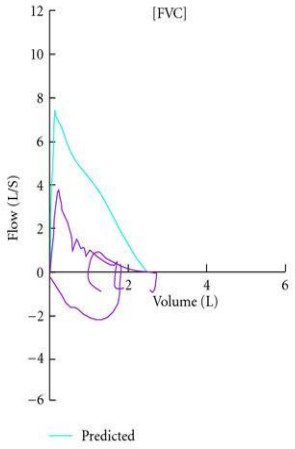
In patients with a history of possible occupational asthma, which of the following is important to establish a diagnosis?

- A. Confirm a diagnosis of asthma objectively
- B. Skin-prick testing where feasible
- C. Induced sputum if available
- D. Peak expiratory flows during and off work
- E. Methacholine challenge at the end of a work week and after a period off work
- F. All of the above

A Case of Asthma 2 (Severe Bronchial Asthma Controlled with Tacrolimus)

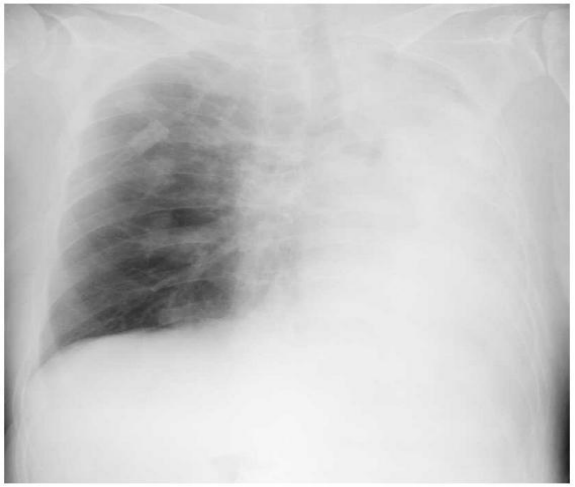
- A 55-year-old Japanese female was admitted with infected traumatic cutaneous ulcers. The infectious organism was *Staphylococcus aureus*, and levofloxacin was administered. She had been diagnosed with bronchial asthma during childhood and had been treated by her family doctor. For several years, her bronchial asthma worsened and she was treated with fluticasone/salmeterol (500 mcg/100 mcg per day), prednisolone (10 mg per day), theophylline (400 mg per day), and pranlukast (leukotriene receptor antagonist, 450 mg per day). She had suffered from dyspnea upon exertion and wheezing continuously for the prior two months. Pulmonary function tests, which had been conducted three months before admission, showed a pattern of obstruction

Pulmonary function test	
VC	2.87 L
%VC	115.7%
TV	1.26 L
FVC	2.91 L
%FVC	119.7%
FEV1	1.37 L
%FEV1	66.5%
FEV1%(Geansler)	47.1%
PEF	3.65 L/sec
%PEF	49.5%
$\dot{V}_{50}$	0.49 L/sec
%$\dot{V}_{50}$	12.6%
$\dot{V}_{25}$	0.15 L/sec
%$\dot{V}_{25}$	8.7%

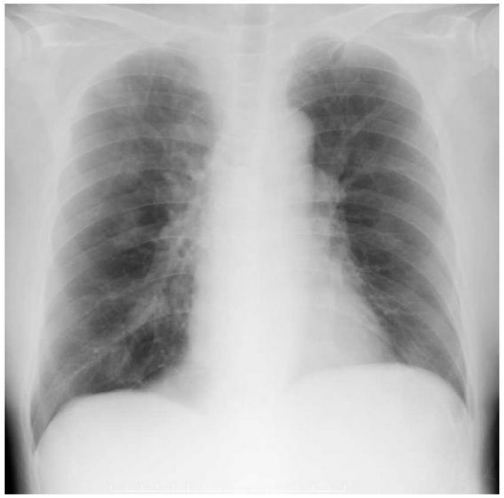


- Her bronchial asthma showed exacerbation after admission. Laboratory studies revealed a serum lactate dehydrogenase (LDH) level of 287 international units (IU) per liter, myeloperoxidase–antineutrophil cytoplasmic antibody (MPO-ANCA) levels less than 1.3 IU per milliliter, and an immunoglobulin E (IgE) level of 635 IU per milliliter; no peripheral blood eosinophils were detected. Her prednisolone dose was increased to 20 mg per day, but she developed dyspnea, wheezing, and hypoxia necessitating inhalation of oxygen. This exacerbation of her bronchial asthma persisted for a month, despite the increase in prednisolone. Next, 300 mg per day of omalizumab was administered; however, her dyspnea persisted and her chest radiograph showed atelectasis of the left lung. Her CRP level was 0.27 mg per liter. Bronchoscopy revealed that the left main bronchus and other left bronchi were obstructed with colorless viscous sputum. Due to the large volume of viscous sputum in the peripheral bronchi, bronchial toileting did not improve the atelectasis. No eosinophils or malignant cells were identified in suction specimens of the sputum, which contained 82% neutrophils and 18% lymphocytes, and no bacteria or fungi were detected by sputum cultures. The prednisolone dose was increased to 120 mg per day for three days and then to 60 mg per day for the remainder of the hospitalization

- Panipenem/betamipron (carbapenem antibiotic) was administered concurrently with the prednisolone treatment for two weeks. However, the patient continued to demonstrate severe dyspnea, wheezing, and hypoxia that required the inhalation of a large amount of oxygen, and her atelectasis did not improve. One month later, she was treated with 2 mg per day of tacrolimus. Her symptoms and respiratory status did not change during the first week, but, thereafter, the atelectasis improved. Thereafter, her dyspnea and hypoxia started to gradually improve. After three months of tacrolimus administration, oxygen administration was stopped and the patient became capable of short walks. The prednisolone was tapered over the course of four weeks to 20 mg per day, and she was transferred to another hospital for rehabilitation.



A chest radiograph showed atelectasis of the left lung.



A chest radiograph showed an improvement in the atelectasis of the left lung.

Diagnosis and Management

- In the current patient, we suspected that the cause of atelectasis was exacerbation of bronchial asthma. This case was not considered to have allergic bronchopulmonary aspergillosis based on negative findings for IgE specific to aspergillus, negative suction sputum cultures, no peripheral blood eosinophils, and no central bronchiectasis. We also ruled out the possibility of allergic bronchopulmonary candidiasis, because the only positive finding was IgE specific to candida. In addition, there were no signs of bacterial infection in her lungs, as demonstrated by negative serum CRP, negative suction sputum specimen cultures, and a lack of response to antibiotic treatment.

- The basic pathology of bronchial asthma is chronic airway inflammation with infiltration of inflammatory cells such as eosinophils. Asthmatics with severe disease have predominantly neutrophilic inflammation, in contrast to asthmatics whose disease is controlled. The significance of neutrophilic inflammation is not apparent, but when such inflammation is not controlled by corticosteroid therapy, there is an association with increased severity in a subset of severe asthma cases. The current patient's suction sputum specimens, which were obtained during bronchoscopy, included many neutrophils but no eosinophils. Therefore, the patient demonstrated severe asthma due to neutrophilic inflammation.

- **Tacrolimus** is an immunosuppressive agent. This drug has a mode of action which is similar to that of cyclosporine, namely due to its ability to inhibit calcineurin in T cells. Some previous studies on humans regarding steroid-dependent asthma treated with oral cyclosporine have been reported. These results, therefore, suggest that cyclosporin might be beneficial in some patients with steroid-dependent asthma, while not being of any benefit in other patients. Tacrolimus suppresses the activation of T cells and the production of interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, granulocyte/macrophage colony-stimulating factor (GM-CSF), interferon-gamma, and other proteins.

- Presented a case of severe bronchial asthma, associated with airway inflammation characterized by neutrophil infiltration, controlled with tacrolimus. Therefore, this drug should be considered for the treatment of severe asthma, including cases demonstrating corticosteroid resistance.

Question 2

The immunological mechanisms of asthma include all of these, except one:

- A. Activation basophilic leukocytes
- B. Hypereosinophilia
- C. activation synthesis reagin
- D. Glucocorticoid deficiency
- E. Hypersensitivity reaction negative type