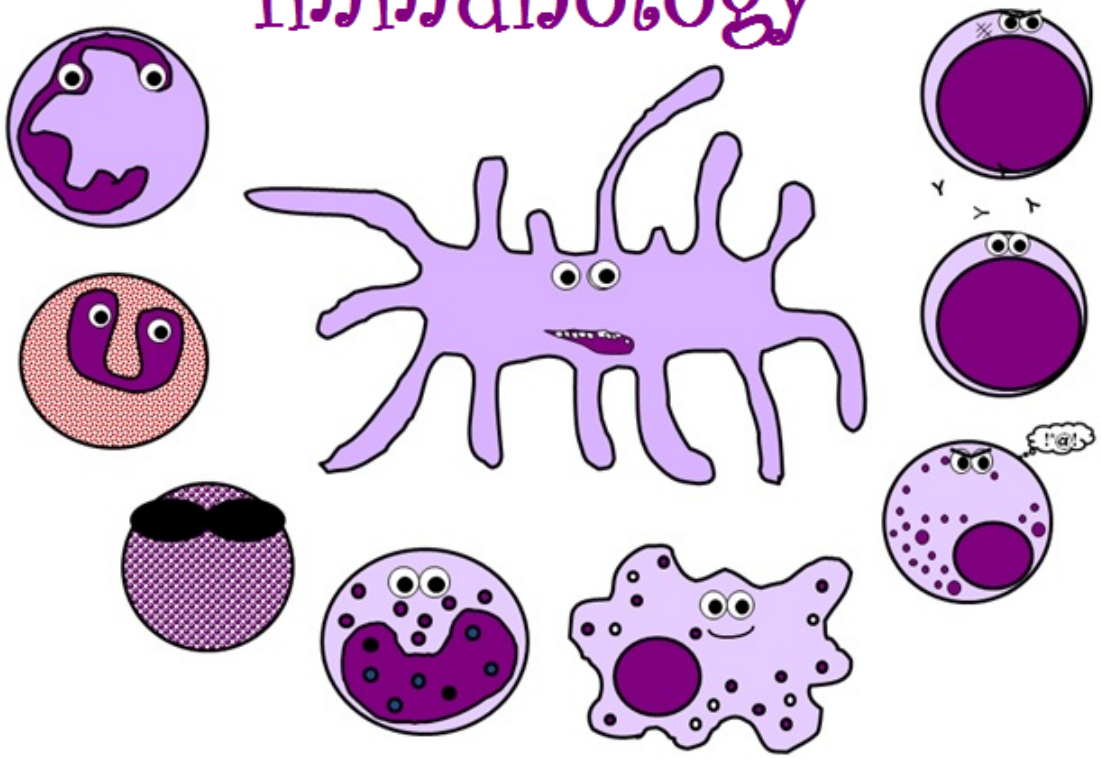
Immunology



Sheet Slides

Number: 18

Subject: Allergic Asthma {case study}

Done by: Mohammad Da'as

Doctor: Issa Abu-Dayyeh

26/11/2016

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{Allergic Asthma}

- The final exam won't be easy, so as a precaution we need to study more details specially in the case studies, this case is easy, study the (Highlighted paragraphs + the figures + doctor's note) and this will be more than enough "inshallah".
- In my slides you'll find some notes under each slide to "ترتيب أفكار ".

VERY Important notes : "read them before you start & After finishing the required book pages"

- It's one of the most common IgE-mediated allergic reactions.
- The route of entry for its Allergen → Inhalation.
- Pollens & Allergens are foreign bodies, our bodies decide not to induce a reaction against them, BUT in case of Allergy → Immune Reaction "allergic Rxn".
- Type 1 Hypersensitivity allergic Reaction.
- Localized to respiratory tract BUT can be fatal.
- Mediated by → T Helper 2 Cells response.
- Main symptoms → (cough & wheezing).
- Genetic predisposition → ATOPY.
- Albuterol → bronchodilator "inhaler"

❖ Sequence of events : "just to know what's waiting for you"

Chronic Allergic Asthma

Allergen → Inhalation → 1st exposure → Armed "sensitized" mast-cell → 2nd exposure → Degranulation "histamine…" → Early phase "an immediate allergic reaction" →Late phase "After 12 hours" → Acute Response →Mucus secretion & smooth muscle contraction → Mediators + cytokines → Cellular Infiltrate → Tissue damage → Chronic response →Obstruction of the Airways → Hyper-sensitivity →Irreversible Damage to Airways.

"هاي هي كل القصة"

☒ More Details will be illustrated through the lecture ☹💣

CASE 50 Allergic Asthma

Chronic allergic disease caused by an adaptive immune response to inhaled antigen.

Chronic allergic reactions are much more common than the acute systemic anaphylaxis reaction discussed in Case 49. Among these are allergic reactions to inhaled antigens (Fig. 50.1), which range in severity from a mild allergic rhinitis (hay fever) to potentially life-threatening allergic asthma, the disease discussed in this case. Once an individual has been sensitized, the allergic reaction becomes worse with each subsequent exposure to allergen, which not only produces allergic symptoms but also increases the levels of antibody and T cells reactive to the allergen.

T cells --> TH2 cells
Abs --> IgE

Allergic asthma is an example of a type I hypersensitivity reaction. Type I reactions involve the activation of helper CD4 T_H2 cells, IgE antibody formation, mast-cell sensitization, and the recruitment of eosinophils. The allergen-specific IgE antibodies formed in sensitized individuals bind to and occupy high-affinity Fcε receptors (FcεRI) on the surfaces of tissue mast cells and basophils (Fig. 50.2). When the antigen is encountered again, it cross-links these bound IgE molecules, which triggers the immediate release of mast-cell granule contents, in particular histamine and various enzymes that increase blood flow and vascular permeability. This is the early phase of an immediate allergic reaction.

first exposure

second exposure

Within 12 hours of contact with antigen, a late-phase reaction occurs (Fig. 50.3). Arachidonic acid metabolism in the mast cell generates prostaglandins and leukotrienes, which further increase blood flow and vascular permeability. Cytokines such as interleukin-3 (IL-3), IL-4, IL-5, and tumor necrosis factor-α (TNF-α) are produced by both activated mast cells and helper T cells, and these further prolong the allergic reaction. The mediators and cytokines released by mast cells and helper T cells cause an influx of monocytes, more

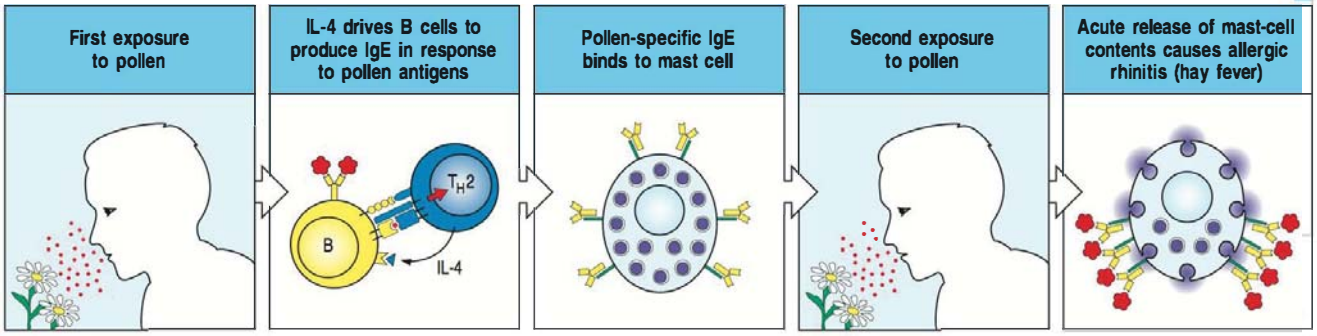
note : refer to table (1) and link it with these products

mediators = CCL3

Topics bearing on this case:

- Inflammatory reactions
- iNKT cells
- Differential activation of T_H1 and T_H2 cells
- IgE-mediated hypersensitivity
- Skin tests for hypersensitivity
- Radioimmunoassay
- Tests for immune function

This case was prepared by Raif Geha, MD, in collaboration with Lisa Bartnikas, MD.



summary

تلخيص كل اللي قبل

Fig. 50.1 Allergic reactions require previous exposure to the allergen. In this example, the first exposure to pollen induces the production of IgE anti-pollen antibodies, driven by the production of IL-4 by helper T cells (T_H2). The IgE binds to mast cells via FcεRI. Once enough IgE antibody is present on mast cells, exposure to the same pollen induces mast-cell activation and an acute allergic reaction, here allergic rhinitis (hay fever). Allergic reactions require an initial sensitization to the antigen (allergen), and several exposures may be needed before the allergic reaction is initiated.

Important

T cells, and eosinophils into the site of allergen entry. The late-phase reaction is dominated by this cellular infiltrate. The cells of the infiltrate, particularly the eosinophils, make a variety of products that are thought to be responsible for much of the tissue damage and mucus production that is associated with chronic allergic reactions. Cytokine-producing NKT cells have also been implicated in allergic asthma.

Approximately 15% of the population suffers from IgE-mediated allergic diseases. Many common allergies are caused by inhaled particles containing foreign proteins (or allergens) and result in allergic rhinitis, asthma, and allergic conjunctivitis. In asthma, the allergic inflammatory response increases the hypersensitivity of the airway not only to allergen reexposure but also to nonspecific agents such as exercise, pollutants, and cold air.

Extrinsic asthma: due to allergen "foreign body" that is inhaled

Intrinsic asthma : "no need for allergen" due to exercise, pollutants and cold air

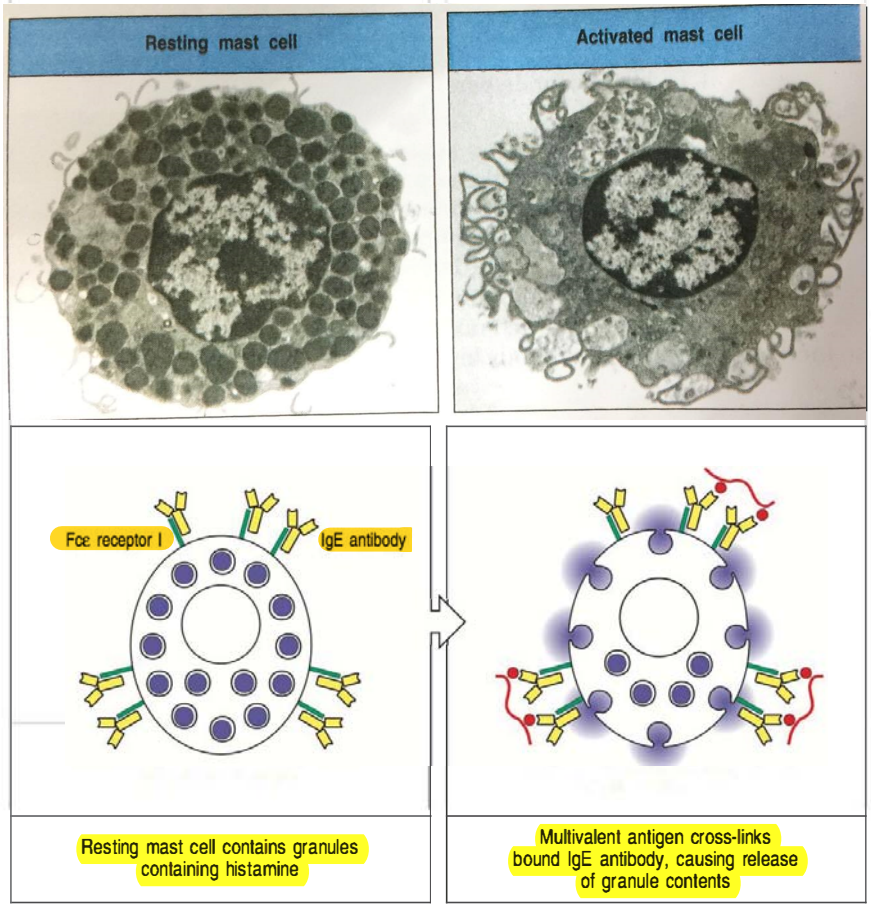


Fig. 50.2 Cross-linking of IgE antibody on mast-cell surfaces leads to a rapid release of inflammatory mediators by the mast cells. Mast cells are large cells found in connective tissue that can be distinguished by secretory granules containing many inflammatory mediators. They bind stably to monomeric IgE antibodies through the very high-affinity Fcε receptor (FcεRI). Antigen cross-linking of the bound IgE antibody molecules triggers rapid degranulation, releasing inflammatory mediators into the surrounding tissue. These mediators trigger local inflammation, which recruits cells and proteins required for host defense to sites of infection. It is also the basis of the acute allergic reaction causing allergic asthma, allergic rhinitis, and the life-threatening response known as systemic anaphylaxis (see Case 49). Photographs courtesy of A.M. Dvorak.

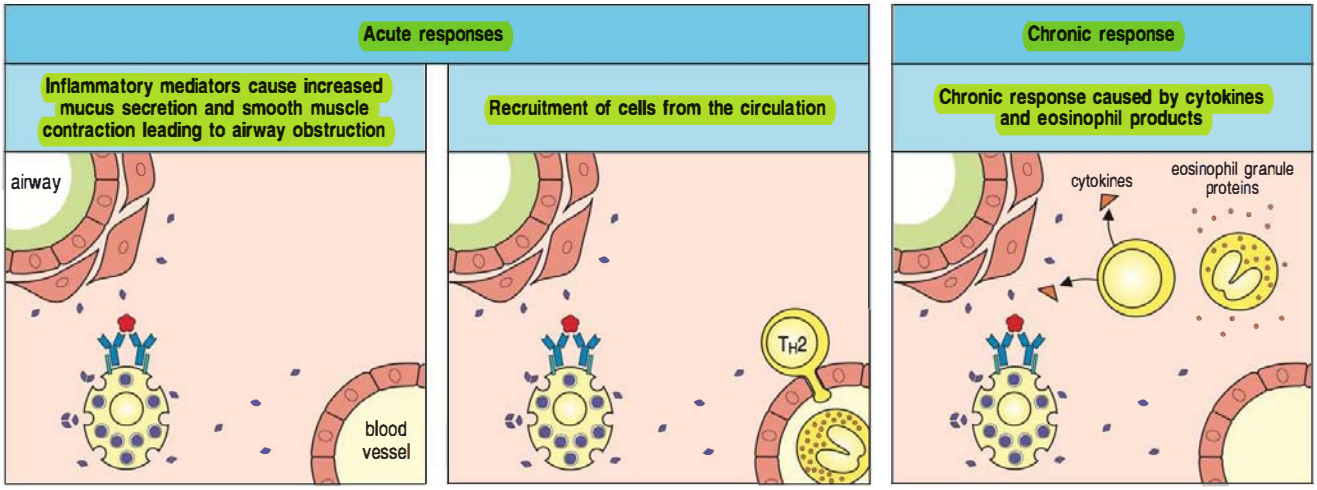


Fig. 50.3 The acute response in allergic asthma leads to T_H2-mediated chronic inflammation of the airways. In sensitized individuals, cross-linking of specific IgE on the surface of mast cells by inhaled allergen triggers them to secrete inflammatory mediators, causing bronchial smooth muscle contraction and an influx of inflammatory cells, including eosinophils and T_H2 lymphocytes. Activated mast cells and T_H2 cells secrete cytokines that also augment eosinophil activation, which causes further tissue injury and influx of inflammatory cells. The end result is chronic inflammation, which may then cause irreversible damage to the airways.

The case of Frank Morgan: a 14-year-old boy with chronic asthma and rhinitis.

Frank Morgan was referred by his pediatrician to the allergy clinic at 14 years of age because of persistent wheezing for 2 weeks. His symptoms had not responded to frequent inhalation treatment (every 2–3 hours) with a bronchodilator, the β_2-adrenergic agonist albuterol.

This was not the first time that Frank had experienced respiratory problems. His first attack of wheezing occurred when he was 3 years old, after a visit to his grandparents who had recently acquired a dog. He had similar attacks of varying severity on subsequent visits to his grandparents. Beginning at age 4 years, he had attacks of coughing and wheezing every spring (April and May) and toward the end of the summer (second half of August and September). A sweat test at age 5 years to rule out cystic fibrosis, a possible cause of chronic respiratory problems, was within the normal range.

As Frank got older, gym classes, basketball, and soccer games, and just going outside during the cold winter months could bring on coughing and sometimes wheezing. He had been able to avoid wheezing induced by exercise by inhaling albuterol 15–20 minutes before exercise. Frank had frequently suffered from a night-time cough, and his colds had often been complicated by wheezing.

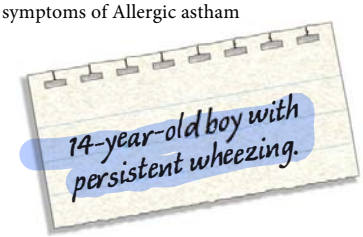
Frank's chest symptoms had been treated as needed with inhaled albuterol. During the previous 10 years, Frank had been admitted to hospital three times for treatment of his asthma with inhaled bronchodilators and intravenous steroids. He had also been to the Emergency Room many times with severe asthma attacks. He had maxillary sinusitis at least three times, and each episode was associated with green nasal discharge and exacerbation of his asthma.

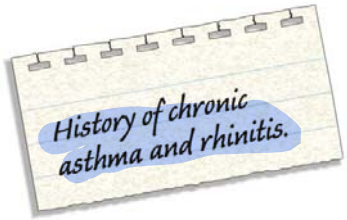
Since he was 4 years old, Frank had also suffered from intermittent sneezing, nasal itching, and nasal congestion (rhinitis), which always worsened on exposure to cats and dogs and in the spring and late summer. The nasal symptoms had been treated as needed with oral antihistamines with moderate success. Frank had had eczema as a baby, but this cleared up by the time he was 5 years old.

Family history revealed that Frank's 10-year-old sister, his mother, and his maternal grandfather had asthma. Frank's mother, father, and paternal grandfather suffered from allergic rhinitis.

Genetic predisposition = Atopy

coughing and wheezing --> main symptoms of Allergic astham





EXTRA NOTE : a syndrome characterized by a tendency to be "hyperallergic". A person with atopy typically presents with one or more of the following : eczema (atopic dermatitis), . allergic rhinitis (hay fever), or allergic asthma

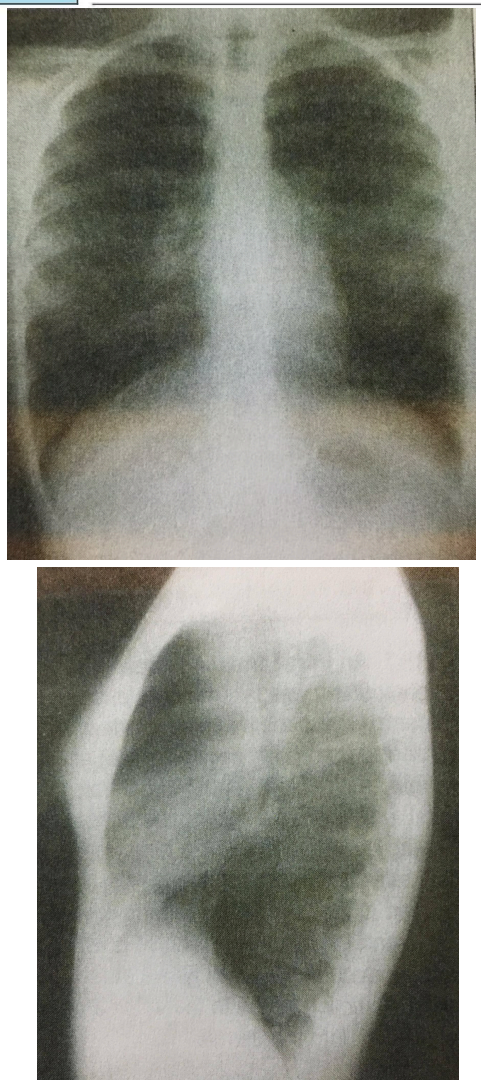


Fig. 50.4 Chest radiographs of a patient with asthma. Top: anteroposterior (A–P) view. Bottom: lateral view. The volume occupied by the lungs spans eight to nine rib spaces instead of the normal seven in the A–P view and indicates hyperinflation. The lateral view shows an increased A–P dimension, also reflecting hyperinflation. Hyperinflation indicates air trapping, which is a feature of the obstructive physiology seen in asthma. The bronchial markings are accentuated and can be seen to extend beyond one-third of the lung fields. This indicates inflammation of the airways.

When he arrived at the allergy clinic, Frank was thin and unable to breathe easily. He had no fever. The nasal mucosa was severely congested, and wheezing could be heard over all the lung fields. Lung function tests were consistent with obstructive lung disease with a reduced peak expiratory flow rate (PEFR) of 180 liter min^{-1} (normal more than 350–400 liter min^{-1}), and forced expiratory volume in the first second of expiration (FEV_1) was reduced to 50% of that predicted for his sex, age, and height. A chest radiograph showed hyperinflation of the lungs and increased markings around the airways (Fig. 50.4).

A complete blood count was normal except for a high number of circulating eosinophils (1200 μl^{-1}; normal range less than 400 μl^{-1}). Serum IgE was high at 1750 ng dl^{-1} (normal less than 200 ng dl^{-1}). Radioallergosorbent assays (RAST) for antigen-specific IgE revealed IgE antibodies against dog and cat dander, dust mites, and tree, grass, and ragweed pollens in Frank's serum. Levels of immunoglobulins IgG, IgA, and IgM were normal. Histological examination of Frank's nasal fluid showed the presence of eosinophils.

Frank was promptly given albuterol nebulizer treatment in the clinic, after which he felt better, his PEFR rose to 400 liter min^{-1}, and his FEV_1 rose to 65% of predicted. He was sent home on a 1-week course of the oral corticosteroid prednisone. He was told to inhale albuterol every 4 hours for the next 2–3 days, and then to resume taking albuterol every 4–6 hours as needed for chest tightness or wheezing. He was also started on fluticasone propionate (Flovent), an inhaled corticosteroid, and montelukast (Singulair), a leukotriene receptor antagonist for long-term control of his asthma. To relieve his nasal congestion, Frank was given the steroid fluticasone furoate (Flonase) to inhale through the nose, and was advised to use an oral antihistamine as needed. He was asked to return to the clinic 2 weeks later for follow-up, and for immediate hypersensitivity skin tests to try to detect which antigens he was allergic to (Fig. 50.5).

Multiple Treatments

On the next visit Frank had no symptoms except for a continually stuffy nose. His PEFR and FEV_1 were normal. Skin tests for type I hypersensitivity were positive for multiple tree and grass pollens, dust mites, and dog and cat dander. He was advised to avoid contact with cats and dogs. To reduce his exposure to dust mites the pillows and mattresses in his room were covered with zippered covers. Rugs, stuffed toys, and books were removed from his bedroom. He was also started on immunotherapy with injections of grass, tree, and ragweed pollens, cat, dog, and house dust mite antigens, to try to reduce his sensitivity to these antigens.

A year and a half later, Frank's asthma continues to be stable with occasional use of albuterol during infections of the upper respiratory tract and in the spring. His rhinitis and nasal congestion now require much less medication.

Allergic asthma.

Like Frank, millions of adults and children suffer from allergic asthma. Asthma is the most common chronic inflammatory disorder of the airways and is characterized by reversible inflammation and obstruction of the small airways. Asthma has become an epidemic; the prevalence in the United States is increasing by 5% per year, with more than 500,000 new cases diagnosed annually. It is the most common cause of hospitalization and days lost from school in children. About 70% of patients with asthma have a family history of allergy. This genetic predisposition to the development of allergic diseases is called atopy. Wheezing and coughing are the main symptoms of asthma, and both are due to the forced expiration of air through airways that have become temporarily narrowed by the constriction of smooth muscle as a result of the

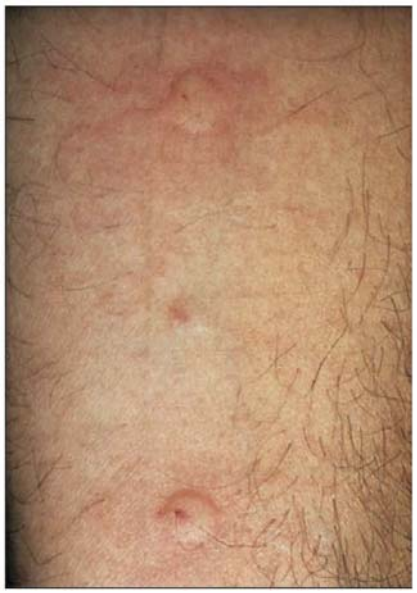


Fig. 50.5 An intradermal skin test. The photograph was taken 20 minutes after intradermal injections had been made with ragweed antigen (top), saline (middle), and histamine (bottom). A central wheal (raised swelling), reflecting increased vascular permeability, surrounded by a flare (red area), reflecting increased blood flow, is observed at the sites where the ragweed antigen and the positive histamine control were introduced. The small wheal at the site of saline injection is due to the volume of fluid injected into the dermis.

allergic reaction. As a consequence of the narrowed airways, air gets trapped in the lung, and the lung volume is increased during an attack of asthma (Fig. 50.6).

Once asthma is established, an asthma attack can be triggered not only by the allergen but by viral infection, cold air, exercise, or pollutants. This is due to a general hyperirritability or hyperresponsiveness of the airways, leading to constriction in response to nonspecific stimuli, thus reducing the air flow. The degree of hyperresponsiveness can be measured by determining the threshold dose of inhaled methacholine (a cholinergic agent) that results in a 20% reduction in airway flow. Airway irritability correlates positively with eosinophilia and serum IgE levels.

CD4 T cells are the central effector cells of airway inflammation in asthma. During asthma exacerbations, secretion of the T_H2-specific cytokines IL-4, IL-5, IL-9, and IL-13 is increased. Clinical improvement in asthma is associated with decreased T cells in the airways. Mast cells are also important effector cells in asthma and, after stimulation by allergen, release preformed and newly generated mediators, contributing to acute and chronic mucosal inflammation. Cysteinyl leukotrienes, a product of arachidonic metabolism, are also key inflammatory mediators in asthma (Fig. 50.7). Cysteinyl leukotriene receptors include at least three types of transmembrane receptors. Activation of the cysteinyl leukotriene receptor 1 ($CysLT_1$) leads to bronchial smooth muscle constriction and muscle-cell proliferation, plasma leakage,

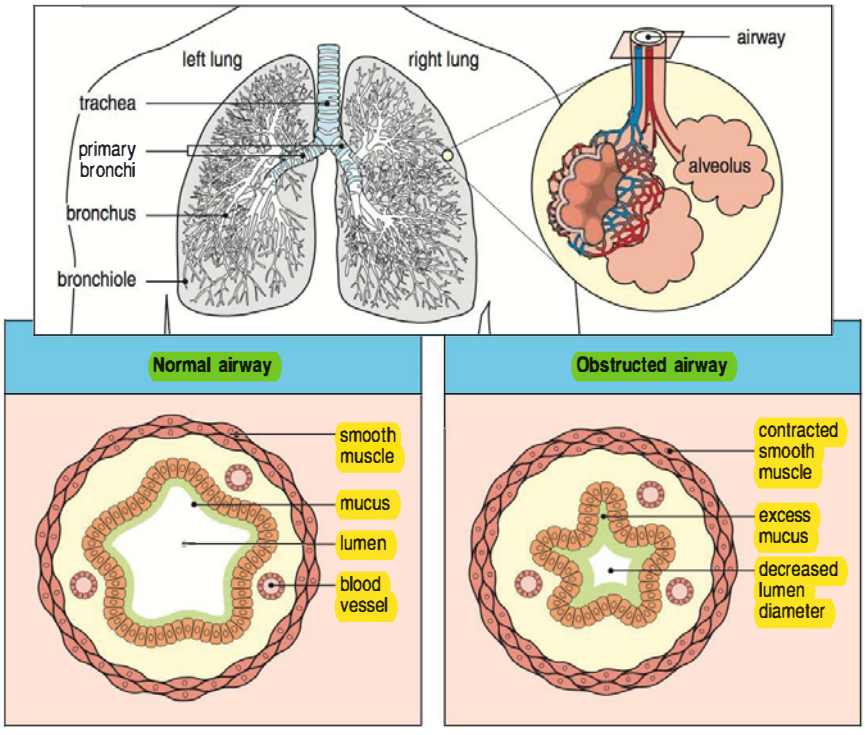
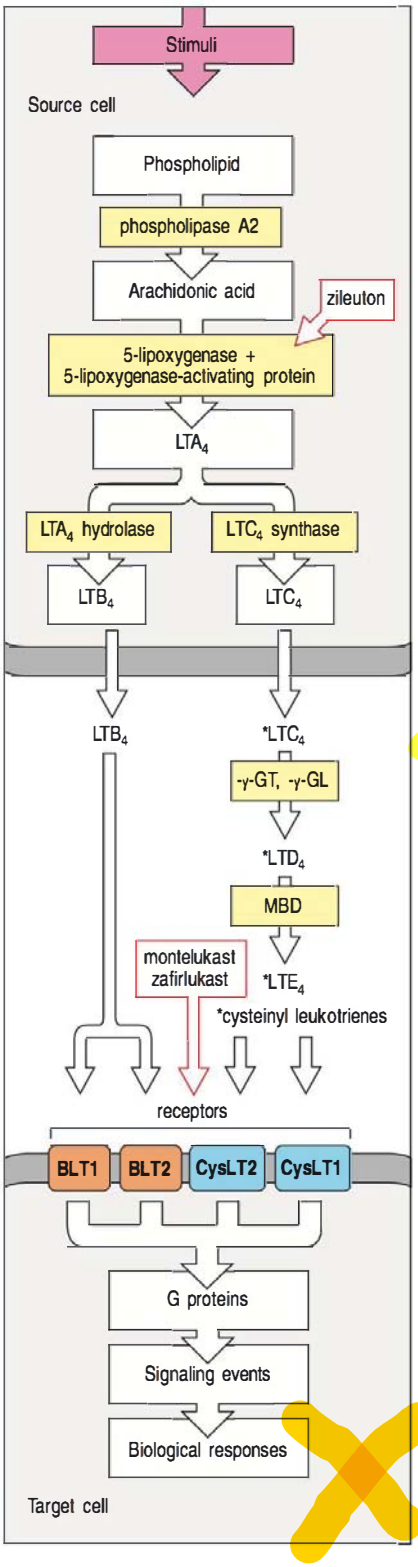


Fig. 50.6 Obstruction of the airways in chronic asthma. The top panels show the general anatomy of the lungs. Asthma is a chronic inflammatory disorder of the small airways—the bronchi and the bronchioles. In susceptible individuals, inflammation leads to recurrent wheezing, shortness of breath, chest tightness, and coughing. In between asthma attacks, patients are often asymptomatic, with normal physical exams and breathing tests. The bottom panels show schematic diagrams of sections through a normal airway (left) and an obstructed airway as a result of chronic asthma (right). During an asthma attack, there is infiltration of blood vessels of the small airways with immune cells (T_H2 lymphocytes and eosinophils), hypersecretion of mucus, and constriction and proliferation of bronchial smooth muscle. This leads to a decreased diameter of the airway lumen, resulting in wheezing and difficulty in breathing. In patients with severe asthma, there may be permanent airway remodeling.



hypersecretion of mucus, and eosinophil migration. The role of neutrophils in asthma is less clear. Elevated neutrophil numbers are more frequently seen in non-allergic asthma, steroid-unresponsive asthma, and in fatal asthma, suggesting that neutrophil-dominated asthma may represent a distinct asthma phenotype. Elevated neutrophil numbers in asthmatic lungs are associated with increased expression of IL-17.

The subset of T cells called invariant NKT cells (iNKT cells) is also elevated in asthmatic airways, suggesting that they may be important in human asthma. iNKT cells are a subpopulation of thymus-derived T cells that express markers of both T cells (such as the T-cell receptor:CD3 complex) and NK cells (such as NK1.1 and Ly-49). In humans, iNKT cells express an invariant antigen receptor with a variable region composed of $V_{\alpha}24$--$J_{\alpha}15$ paired with $V_{\beta}11$. Unlike conventional T cells, iNKT cells can recognize glycolipid antigens bound and presented by the major histocompatibility complex (MHC) class Ib molecule CD1d. On activation, iNKT cells rapidly produce large amounts of the T_H1-type cytokine IFN-γ, the T_H2-type cytokines IL-4 and IL-13, and TNF-α and IL-2. The trigger for their activation in people with asthma could be glycolipids derived from microbes colonizing asthmatic airways.

Although asthma is a reversible disease, severe uncontrolled asthma can lead to airway remodeling, and a severe attack can be fatal. The mortality from asthma has been rising alarmingly in recent years. Risk factors for fatal asthma include frequent use of β_2-agonist therapy, poor perception of asthma severity, membership in a minority group, low socioeconomic status, adolescence, and male gender.

Several classes of drugs are commonly used to treat asthma, including corticosteroids, leukotriene antagonists, anti-IgE antibodies, anticholinergics, and β_2-adrenergic agonists. Corticosteroids (oral prednisone and inhaled fluticasone) inhibit the transcription of allergic and pro-inflammatory cytokines and can also activate the transcription of anti-inflammatory cytokines. This leads to a decrease in the numbers of mast cells, eosinophils, and T lymphocytes in the bronchial mucosa. Leukotriene antagonists (zileuton, montelukast, and zafirlukast) inhibit the synthesis of leukotrienes (which are products of arachidonic acid metabolism) or their receptor binding (see Fig. 50.7). Leukotriene modifiers have both mild bronchodilator and anti-inflammatory properties. Anti-IgE therapy uses a humanized monoclonal antibody (omalizumab) directed against the IgE that forms complexes with free IgE and prevents its biding to the receptor FcεRI on the surfaces of mast cells and basophils. This results in a decrease in circulating free IgE and the downregulation of FcεRI expression on the cell surfaces. β_2-agonists (for example albuterol) bind to the β_2-adrenergic receptor, which is expressed on the surface of bronchial smooth muscle cells. β_2-agonists relax smooth muscle, thus rapidly relieving airway constriction, and are helpful in treating the immediate phase of the allergic reaction in the lungs. The treatment of allergic asthma also includes minimizing exposure to allergens and, in cases of severe or refractory environmental allergies, trying to desensitize the patient by immunotherapy.

summarized by the doctor in a great way

Fig. 50.7 Leukotriene synthesis pathways and receptors. The biosynthetic pathway leading from arachidonic acid to the various leukotrienes is shown here, along with the sites of action of drugs used in asthma to block leukotriene synthesis and action (shown in red boxes). γ-GL, γ-glutamyl leukotrienase; γ-GT, γ-glutamyl transferase; MBD, membrane-bound dipeptidase. BLT1, BLT2, CysLT2, and CysLT1 are receptors.

Questions.

1 Explain the basis of Frank's chest tightness and the radiograph findings.

2 Explain the failure of Frank's asthma to improve despite the frequent use of bronchodilators, and his response to steroid therapy.

3 Eosinophilia is often detected in the blood and in the nasal and bronchial secretions of patients with allergic rhinitis and asthma. What is the basis for this finding?

4 What is the basis of the wheal-and-flare reaction that appeared 20 minutes after Frank had had a skin test for hypersensitivity to ragweed pollen?

5 Frank called 24 hours after his skin test to report that redness and swelling had recurred at several of the skin test sites. Explain this observation.

6 Frank developed wheezing on several occasions after taking the nonsteroidal anti-inflammatory drugs (NSAIDs) aspirin and ibuprofen (Motrin). Explain the basis for these symptoms.

7 How would the immunotherapy that Frank received help to alleviate his allergies?

8 Although atopic children are repeatedly immunized with protein antigens such as tetanus toxoid, they almost never develop allergic reactions to these antigens. Explain.

Doctor Notes

- ✓ Type 1 IgE-mediated hypersensitivity reaction localized to respiratory tract but can be **fatal** ☠.
- ✓ Mediated by a Th2 response → TH2 cytokine profile "IL-4" is mainly responsible for → **Class switch of IgE**.
- ✓ IgE → **Arming** of mast cells + Basophils, **recruitment of Eosinophils** …
- ✓ Allergic Rxn which is done after the 2nd Exposure!!
- ✓ **Eosinophilia** is mostly related with **chronic diseases**

❖ Allergic Asthma has → **Acute** phase & **Chronic** phase.

1. **Acute** phase: initial phase of exposure, mast cell recruitment, production of Histamine → Mucus secretion & Bronchoconstriction.
2. **Chronic** phase: further cell infiltration "TH2, Eosinophils" → further tissue damage of the airways even if there was no bronchoconstriction.

Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T_H2 cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
Chemokine	MIP-1α CCL3	Attracts monocytes, macrophages, and neutrophils
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Fig. 19.4 cells on a wide variet other cher toxic medi are releas The cytok mediators

Table (1):

Molecules Released by Mast Cell on Activation

** Chemokine → attracts immune cells

** CCl3 → it contains two adjacent Cystienes

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Serum Venoms	Intravenous (either directly or following oral absorption into the blood)	Edema Vasodilation Tracheal occlusion Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhaled	Edema of nasal mucosa Irritation of nasal mucosa
Allergic asthma	Danders (cat) Pollens Dust-mite feces	Inhaled	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Shellfish Milk Eggs Fish Wheat	Oral	Vomiting Diarrhea Pruritus itching Urticaria (hives) Anaphylaxis (rarely)

Table (2):

IgE-mediated allergic reactions

** due to Atopy→ patient will have Allergic Rhinitis "التهاب الأغشية المخاطية".

- RAST test is no more used → because of using radiolabel materials.
- The new tests are called → **Specific IgE allergy testing.**

Case of Frank Morgan

- 14 year-old, wheezing for 2 weeks.
- History of wheezing and respiratory problems.
- Family History of asthma (Genetic causes)= **Atopy**
- Normal CBC except for **eosinophilia**
- **Elevated serum IgE.**
- **Pulmonary Function Test :** "blowing in a tube"
  - Reduced peak flow rate (PFR).
  - Reduced expiratory volume in the first second (FEV1).

- Multiple treatments
- **Skin prick** test 2 weeks later for inhalants because of→ **<u>Tachyphylaxis</u>**
  - There must be Negative control "Saline".
  - Positive Control "Histamine".
  - Allergens will cause → wheal "إنتفاخ" and flare "إحمرار".
- Started on **<u>immunotherapy</u>** for pollens and dust mites will lead to → **Desensitization** for allergen.

Treatment of Asthma

Three classes of drugs commonly used:

1- **Disodium Cromoglycate**: Reduced airway irritability by → inhibiting the release of chemical mediators such as: Histamine. **(Immediate and late phases)**
2- **β2 agonists** (**Albuterol**): "bronchodilator" binds to receptors on the surface of bronchial smooth muscle cells causing them to relax. **(Immediate phase)**
3- **Corticosteroids** ex: (Oral prednisone and inhaled beclomethasone) Inhibit cells involved in airway inflammation **(Late Phase)**.
4- Minimize exposure to allergens.
5- Immunotherapy.

Questions

1- Explain and Hyperinflation of lungs in X-rays and chest pain?

Narrowing of airways in asthma causes air to be **trapped** in lungs (**Hyperinflation**). Breathing at high residual lung volume → **more work to muscles** and **increased energy expenditure**→ Chest tightness

2- Why didn't Frank asthma improve with bronchodilators?

Chronic Allergic asthma is more due to **inflammation** "late phase", than bronchoconstriction.

3- Several members of Frank's family are atopic, what's the basis for this familial predisposition?

Atopy maps to **chromosome 5q** in areas coding for → **IL-4, IL-5**, and IL-9.

4- How do we explain eosinophilia in blood and nasal/bronchial secretions of patients with allergic rhinitis and asthma?

IL-4, IL-5 production by Th2, **eotoxin** production by T cells and **bronchial epithelial cells**

5- 24 hours after skin prick test, Frank called hospital worried that redness and swelling had recurred at several skin test sites, explain?

Beginning of **Late-phase** response, this is characterized by cellular infiltrates.

6- Frank wants to buy a rabbit as a pet and demands a skin-prick test for rabbits, should we go along with his idea?

No → Atopic people are prone to developing **IgE Abs** to numerous allergens. Skin prick result is irrelevant "حتدفع مصاري على الفاضي".

7- How can immunotherapy help alleviate Frank's allergies?

S.C. Injection of high doses of (allergens) is thought to favor antigen presentation of cells **producing IL-12**. **Favoring a Th1 response**, IFN- γ production, and a skew towards IgG production. **IgG competes with IgE**, and Th1 cytokine profile **blocks further IgE production**.

8- Why don't atopic children develop allergic reactions against immunization with protein antigens such as tetanus toxoid?

S.C. Injection of large doses of (antigens) favors a **Th1 response**. Th2 responses usually arise from small, highly soluble protein molecules that are presented to the immune system via mucosal route at very low doses.

Hala Madrid

Y Nada Más