DELAYED ALLERGIC REACTIONS

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BACKGROUND

Delayed hypersensitivity reactions are inflammatory reactions initiated by mononuclear leukocytes. The term delayed is used to differentiate a secondary cellular response, which appears 48-72 hours after antigen exposure, from an immediate hypersensitivity response, which generally appears within 12 minutes of an antigen challenge. These reactions are mediated by T cells and monocytes/macrophages rather than by antibodies. They are also termed type IV hypersensitivity reactions.

Delayed hypersensitivity is a major mechanism of defense against various intracellular pathogens, including mycobacteria, fungi, and certain parasites, and it occurs in transplant rejection and tumor immunity. The central role of CD4+ T cells in delayed hypersensitivity is illustrated in patients with AIDS

Coombs and Gel classified type IV hypersensitivity reaction (HR) as a delayed hypersensitivity reaction (DHR), which takes more than 12 hours to develop. Typically the maximal reaction time occurs between 48 to 72 hours. Antibodies do not mediate DHR; it is mediated by T cells that cause an inflammatory reaction to either exogenous or autoantigens. This HR to exogenous antigens involves T cells and also antigen-presenting cells (APC) such as macrophages and dendritic cells, all produce cytokines that stimulate a local inflammatory response in a sensitized individual. The DHR to autoantigens can be seen in type 1 diabetes mellitus, which is an autoimmune disease that results from autoimmune cell-mediated destruction of insulin-secreting pancreatic beta cells. DHR cannot be transferred from an animal to another by means of antibodies or serum. However, it can be transferred by T cells, particularly CD4 Th1 cells, but it is progressively lost in individuals with HIV/AIDS. Antigen-presenting cells (APC) such as Langerhans cells engulf process and present antigens to antigen-specific T cells that become sensitized. Cytokines produced by keratinocytes, APC, and T cells recruit antigen-nonspecific T cells and macrophages to participate in a local inflammatory reaction. The activity describes the interprofessional evaluation and management of patients with delayed hypersensitivity reactions.

Objectives:

• Describe the signs and symptoms of delayed hypersensitivity reactions.

• Identify how the diagnosis of delayed hypersensitivity reaction is confirmed.

• Explain treatment considerations for patients with a delayed hypersensitivity reaction.

• Outline the importance of enhancing care coordination among the interprofessional team to ensure proper evaluation and management of DHR.

Introduction

Coombs and Gel classified type IV hypersensitivity reaction (HR) as a delayed hypersensitivity reaction (DHR), which takes more than 12 hours to develop. Typically the maximal reaction time occurs between 48 to 72 hours. Antibodies do not mediate DHR; it is mediated by T cells that cause an inflammatory reaction to either exogenous or autoantigens. This HR to exogenous antigens involves T cells and also antigen-presenting cells (APC) such as macrophages and dendritic cells, all produce cytokines that stimulate a local inflammatory response in a sensitized individual. The DHR to autoantigens can be seen in type 1 diabetes mellitus, which is an autoimmune disease that results from autoimmune cell-mediated destruction of insulin-secreting pancreatic beta cells. DHR cannot be transferred from an animal to another by means of antibodies or serum. However, it can be transferred by T cells, particularly CD4 Th1 cells, but it is progressively lost in individuals with HIV/AIDS. Antigen-presenting cells (APC) such as Langerhans cells engulf process and present antigens to antigen-specific T cells that become sensitized. Cytokines produced by keratinocytes, APC, and T cells recruit antigen-nonspecific T cells and macrophages to participate in a local inflammatory reaction.

There are three variants of delayed hypersensitivity as listed below and their maximal reaction time appears in brackets:

• Contact (48 to 72 hours)
• Tuberculin (48 to 72 hours)
• Granulomatous (21 to 28 days)

Etiology

The three types of DHR can distinguish one to another according to the skin reactivity they produce once antigens applied epicutaneously or intradermally. The magnitude of the reaction can be assessed in animals by measuring the thickening of the skin, which is local but also systemic such as cytokine synthesis and T-cell division.

In contact dermatitis, small antigens called haptens penetrate the skin and combine with tissue protein and mediate immune reactions. Langerhans cells are the principal antigen-presenting cells involved in the recognition of hapten-tissue protein complexes and their presentation to T cells. Also, keratinocytes, which express MHC class II molecules and intercellular adhesion molecule-1 (ICAM-1), make a group of cytokines including IL-1, IL-6, IL-8, among others that help in the establishment of the contact hypersensitivity response.[6]

Tuberculin-type hypersensitivity, initially described by Koch, occurs in patients with tuberculosis (TB) or those vaccinated against tuberculosis when they are injected subcutaneously with tuberculin (a product derived from the tubercle bacillus). They react with skin induration, swelling, and redness. Other antigens from several pathogens

can cause a similar reaction in sensitized individuals, including antigens from Leishmania tropica and Mycobacterium leprae.

Granulomatous-type hypersensitivity results from the persistence within macrophages of intracellular pathogens or other substances that the cell is unable to process or destroy. It occurs to a variety of antigens, including beryllium, talc, silica, among others, where macrophages are unable to digest them. In allergic alveolitis, the APC is unable to process and assimilate the immune complexes, and granuloma develop. Another disease is sarcoidosis, where the antigen is unknown but leads to granuloma formation.

Epidemiology

Drug resistance is a challenge for the global control of tuberculosis. A multicentre cohort study was done in the Democratic Republic of the Congo, Cote d'Ivoire, Kenya, Nigeria, Peru, South Africa, and Thailand. Patients were stratified by tuberculosis drug resistance and HIV status. Phenotypic drug susceptibility testing was performed locally. The researchers examined mortality during treatment considering drug susceptibility test results and multivariable logistic regression models adjusting for age, sex, HIV status, and sputum microscopy.

The results showed that inaccurate drug susceptibility testing leads to under-treatment of drug-resistant tuberculosis as well as increased mortality. Rapid molecular drug susceptibility test is required to improve outcomes in patients with MDR tuberculosis. This study showed that 163 (26%) of MDR microorganisms were isolated.

M. leprae drug resistance could affect leprosy treatment success. Studying M. leprae efflux pumps as targets for drug development will enhance the global efforts to eradicate endemic leprosy, and stop the emergence of drug resistance in endemic countries.

Histopathology

In contact hypersensitivity, there are mononuclear cells infiltrates present in both dermis and epidermis. The last one is pushed outward, and a microvesicle forms within it as a consequence of the edema developed. In tuberculin-type sensitivity histologically, there is a dense dermal infiltrate of leukocytes visualized with hematoxylin and eosin (H and E) stain. There is also marked caseation and necrosis within the granuloma. In granulomatous-type hypersensitivity, histology shows a typical epithelioid-cell granuloma. Also, giant cells are visible in the center of the lesion, which is surrounded by a cuff of lymphocytes. The reaction is due to the persistence of the mycobacterial antigen. Mature tissue macrophages can surround the granuloma and are visualized by antibody staining techniques.

History and Physical

Delayed hypersensitivity diseases can develop in humans due to mycobacteria, protozoa, and fungi, although in another granulomatous disease such as Crohn disease,

no infectious microbes have been found. Some of the most critical diseases include leprosy, tuberculosis, schistosomiasis, sarcoidosis, and Crohn disease.

Leprosy is divided clinically into three essential types: tuberculoid, borderline, and lepromatous. In tuberculoid leprosy, the affected skin has a few, well-defined, hypopigmented patches that show epithelioid infiltrate with no microorganisms. In lepromatous shows, multiple confluent skin lesions characterized by numerous bacilli. Borderline leprosy shows physical findings of the two others.

Tuberculosis in the lungs causes a granulomatous reaction that leads to cavitation and the spread of bacteria. There are extensive areas of fibrosis that can see in the chest x-ray. This lesion is typically granulomatous.

Schistosomiasis causes by schistosomes, once the body is sensitized by a granulomatous reaction developed in the parasitized tissue mediated by Th2 lymphocytes.

Sarcoidosis is a chronic and idiopathic disease in which activated macrophage and granuloma accumulate in many tissues along with fibrosis. The condition can be characterized by the presence of enlarged lymph nodes, which may be identified in chest radiographs. This disease is associated with depression of cell-mediated immunity both in vivo and in vitro. A tuberculin test is negative in this disease. The clinical manifestations include granuloma development in the lungs, lymph nodes, nervous system, bones, and skin and are associated with fever, malaise, and shortness of breath due to lung fibrosis.

Crohn disease is another granulomatous disease that is not caused by a microorganism. Granulomas are prominent. It is a chronic disease that affects ileum and colon, and where T-helper cells and APC accumulate in all layers of the intestines.

Evaluation

These reactions can be diagnosed by a skin test of delayed hypersensitivity using antigens and confirmed by history and clinical presentation. For example, the tuberculin test in a patient with pulmonary tuberculosis can give an overwhelming reaction, but this would not occur in a patient with sarcoidosis. A patient should be tested with an array of allergens to prove which of them is causing the problem. The culture of microorganisms can be useful in demonstrating the cause of the delayed hypersensitivity disorder, especially for tuberculosis (sputum culture). Histopathology can be of chief importance in making a diagnosis of a DH reaction or disease. The suspected tissue can be biopsied to prove the nature of the disease and treated accordingly. Immunological testing should be carried out routinely and include complete blood cell count (CBC), T-cell subpopulation, radioallergosorbent test (RAST), and other tests include serology, chest x-ray, body radiographs, and also diagnostic ultrasound and computed tomography (CT) scan.

Treatment / Management

Treatment of type 4 HR involves the treatment of the elicitating cause.

The most common drugs to treat tuberculosis include isoniazid, rifampin, ethambutol, and pyrazinamide. For drug-resistant TB, a combination of antibiotics such as amikacin, kanamycin, or capreomycin for 20 to 30 months should be used.

The most common drugs to treat leprosy include rifampicin and clofazimine in combination with dapsone for multibacillary leprosy. A single dose of antimicrobial combination to cure single lesion paucibacillary leprosy comprises ofloxacin (400 mg), rifampicin (600 mg), and minocycline (100 mg).

Praziquantel can be useful for treating infections caused by all Schistosoma species.

Hydroxychloroquine and chloroquine can use in the therapy of sarcoidosis involving the skin, lungs, and the nervous system.

The use of anti-TNF monoclonal antibodies such as adalimumab and certolizumab have been approved for Crohn disease.

Differential Diagnosis

One of the most critical differential diagnoses in DHR is to rule out sarcoidosis from tuberculosis. Both cause a granulomatous reaction and have many things in common, but the cause of tuberculosis is a microbe that can isolate in the laboratory, which is Mycobacterium tuberculosis. Sarcoidosis is a non-infectious form of the granulomatous disease, and therefore, the culture of lesions will render non-pathogenic bacteria or another type of microbe. Primary T-cell immunodeficiency and hematologic malignancies are also considered in the differential diagnosis. Some of the diseases to consider are as follows:

- DiGeorge Syndrome
- Hodgkin Lymphoma
- Severe Combined Immunodeficiency
- Tuberculosis
- Wiskott-Aldrich Syndrome
- HIV infection
- Measles infection

Prognosis

The prognosis of tuberculosis is better if the disease can diagnose and promptly treat with the antimicrobials. Leprosy can also be a curable disease, but it depends on the stage of this disease and patient compliance with multidrug therapy (MDT). Some skin lesions may persist after treatment. Schistosomiasis is associated with high morbidity both as acute and chronic illness. The prognosis of sarcoidosis is guarded, and the overall death rate is less than 7%. Some patients may require treatment if a complication such as pneumonia and nephropathy develops. Crohn disease has a reserved prognosis; it cannot be cured.

Complications

Complications of Tuberculosis

- Back pain and stiffness

• Tuberculous arthritis
• Heart, liver, and kidney diseases
• Meningitis

Complications of Leprosy Without Treatment

• Permanent damage to skin, nerves, nose, and limbs
• Claw-like hands
• Nosebleeds

Complications of Schistosomiasis

• Gastrointestinal (GI) bleeding and obstruction
• Nephropathy
• Hematuria
• Hemospermia

Complications of Sarcoidosis

• Pneumonia
• Eye problems (cataracts, glaucoma, and blindness)
• Kidney failure
• Neurosarcoidosis (bilateral facial palsy)
• Hypercalcemia

Complications of Crohn Disease

• Obstruction of the small intestine or colon
• Intestine perforation
• Intestinal abscesses and fistulae
• Intestinal bleeding

Pearls and Other Issues

Other diseases that can involve delayed hypersensitivity reactions

In all of them, Th1 cells play a role in responding to autologous antigens leading to autoimmune disease and inflammation.

• Autoimmune myocarditis
• Type 1 diabetes mellitus
• Peripheral neuropathies
• Hashimoto thyroiditis
• Multiple sclerosis
• Rheumatoid arthritis

Some drugs can also cause type IV hypersensitivity reactions. Allopurinol and lamotrigine have a risk of developing delayed hypersensitivity reactions at higher doses.

Enhancing Healthcare Team Outcomes

an interprofessional team evaluates the patient with a delayed hypersensitivity disorder. The family doctor monitors the patient in the community and transfers the patient to an allergist, infectious disease specialist, or immunologist when the essential treatment does not help. In some cases, psychological support is needed. Nurses play a

critical role in the management of a patient with delayed hypersensitivity disorder. they are involved in patient education, supervising treatment, and relating changes in patient status to the team. Pharmacists review medication choices and doses, monitor compliance, and provide patient education. When there is an emergency, e.g., penicillin allergy reaction the entire professional team including physicians and nurses must be involved in care.