Type III Hypersensitivity: Immune-Complex Disease

By Terry O. Harville, MD, PhD

TYPE III hypersensitivity is the third histopathologic observation described in 1963 by Gell and Coombs' classification of drug allergies into four pathophysiological types. In contrast to type I that is due to IgE and type II that can be due to IgG, IgA or IgM, but primarily IgG and IgM with complement activation binding directly to tissue targets, type III can be due to IgG, IgA or IgM binding to targets small enough to circulate in the blood. Commonly, though, these immune complexes of immunoglobulin target material, and frequently with complement proteins, will deposit out

Figure 1. Linear or Smooth Pattern of Antibodies in Type II Hypersensitivity

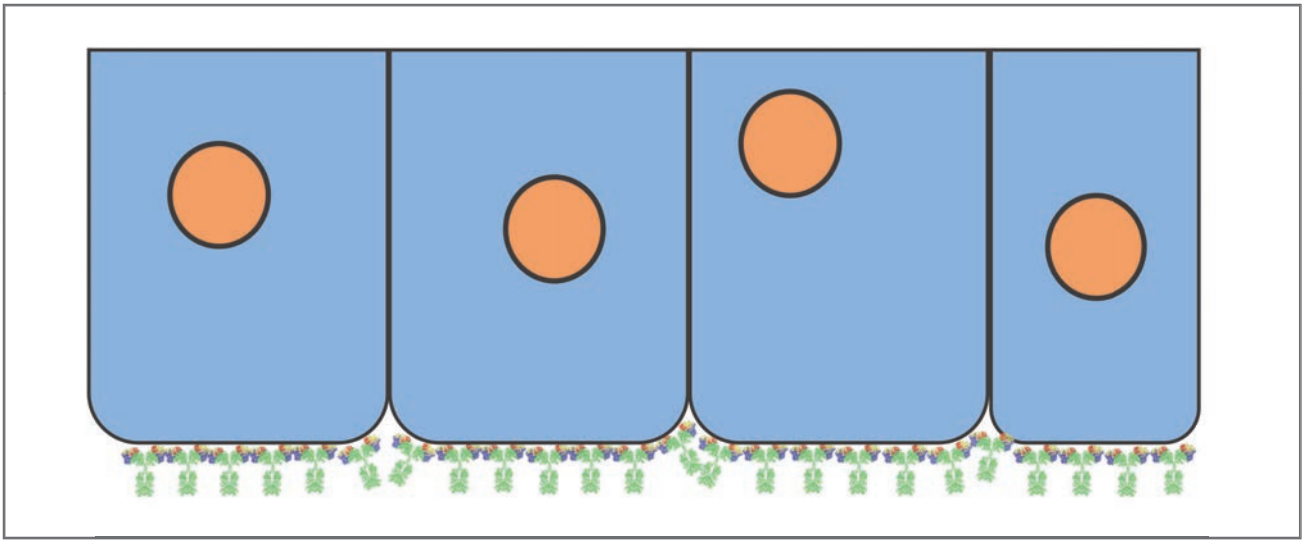

Figure 2. Lumpy-Bumpy Pattern of Immune Complexes in Type III Hypersensitivity

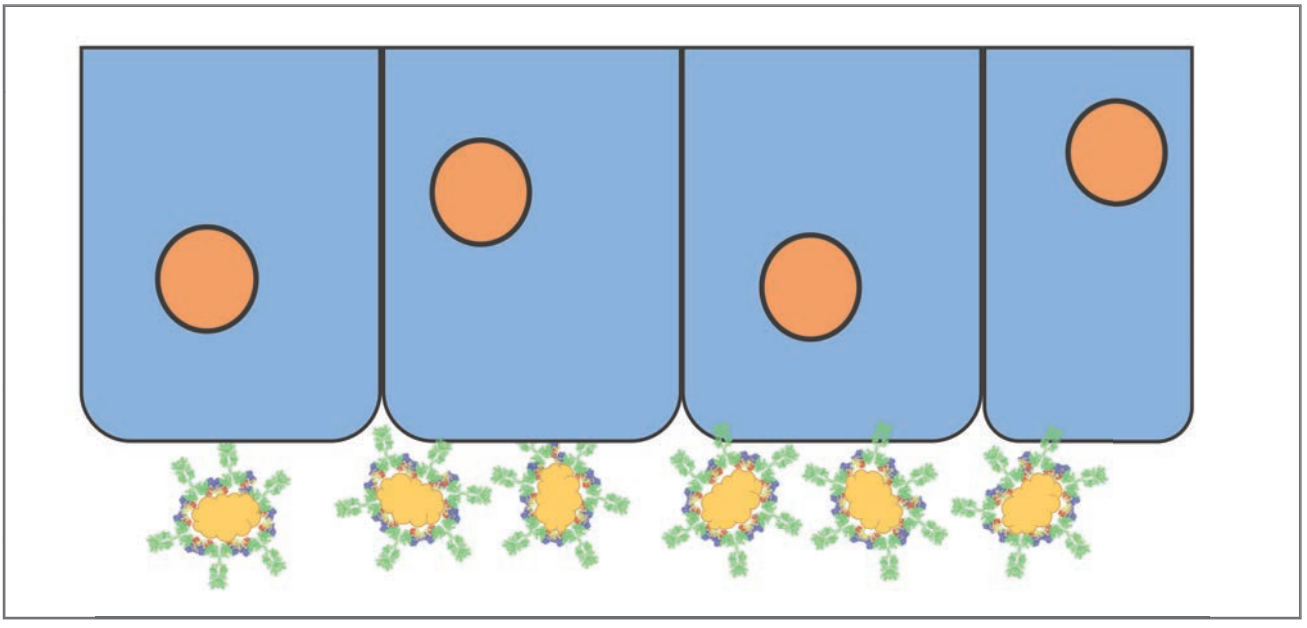

Table. Clinical Manifestations of Common Type II Hypersensitivity Reactions

Disease	Target	Clinical Manifestation(s)
Arthus reaction	Vaccine ingredients	Vasculitis in subcutaneous tissues
Henoch–Schönlein purpura	Unknown/thought to be due to viral infections	IgA antibodies result in purpuric lesions (essentially limited areas of vasculitis)/ glomerulonephritis/gastrointestinal vasculitis
Hypersensitivity pneumonitis	Molds and allergens	Inflammation in the lungs
Polyarteritis nodosa	Hepatitis B virus/other	Vasculitis of medium to small blood vessels
Post-streptococcal glomerulonephritis	Streptococcal antigens	Glomerulonephritis
Reactive arthritis (post-infectious arthritis)	Streptococcus/mycoplasma/shigella /samonellla/campylobacter/other	Swelling, redness, limited mobility and pain in joints and soft tissues around joints
Rheumatoid arthritis	IgG and IgA	Rheumatoid factor (anti-IgG or anti-IgA IgM) binds to IgG and IgA in the plasma/marker of disease/may not cause direct problems
Serum sickness	Animal-derived antitoxins/ post-infectious antigens/other	Joint involvement arthritis/ glomerulonephritis/vasculitis
Systemic lupus erythematosus	dsDNA	dsDNA-anti-dsDNA immune complexes deposit in kidneys resulting in glomerulonephritis

of the bloodstream into tissues. When viewed under the microscope, the type II antibody binding is described as "linear or smooth" since the antibodies frequently bind to cell surfaces or the connective tissues around the cells (Figure 1). On the other hand, the microscopic description of type III is "lumpy-bumpy" due to the aggregates that collect in the tissue space near cells (Figure 2).

Type III hypersensitivity, also known as immune-complex disease, is the deposition of these immune complexes into specific organs that results in disease. For example, after streptococcal infection, some patients develop immune complexes of anti-streptococcal antibodies and proteins from Streptococcus. If these antibodies deposit in the kidney glomeruli, activation of complement in the immune complexes can damage nearby cells and cause blood to leak into the urine, which is known as post-streptococcal glomerulonephritis. Fortunately, in most, this is short-lived and full recovery occurs; however, in some, kidney failure can ensue. In similar fashion, anti-dsDNA antibodies immune complexing with dsDNA can deposit in the kidney glomeruli in patients with systemic lupus erythematosus (SLE), and with activation of complement can also cause glomerulonephritis. Unfortunately, this process results in continuing kidney injury and can result in kidney failure in these patients. Thus, this is generally the most concerning issue in patients with SLE.

Serum sickness is perhaps most commonly associated with type III hypersensitivity. Prior to antibiotics, it was determined that Streptococci cause scarlet fever. Further, it was recognized something in the blood could fight Streptococci (later established to be antibodies). This defense involves injecting heat-killed Streptococci into horses to generate antibodies against the Streptococci proteins. The serum obtained from horses can be injected into someone with scarlet fever, resolving the disease. In some patients, if they later received another dose of horse serum, they would develop fever, rash, joint aches, swelling and blood in the urine, a condition called serum sickness. Subsequently found to be an immune-complex disease, this process can be triggered by a myriad of items, not just serum. The Table lists common type III hypersensitivities.

Type III hypersensitivity is commonly known as serum sickness, and it is at the root of a variety of disease manifestations. Features of vasculitis, arthritis and glomerulonephritis are common outcomes. Treatment is based on reducing the inflammatory processes that have been induced and waiting for the offending item to wane from the body (for example, loss of the Streptococcal protein antigens). In some instances, active therapy is required to stop formation of or to remove the offending antigens, but this may be difficult to achieve. Rarely, a person with hypogammaglobulinemia can have an offending antigen in his or her body, and upon receiving intravenous immune globulin can develop type III hypersensitivity in the form of serum sickness, which is expected to improve as the offending antigen wanes in the body.

In the next issue, we will begin with a discussion of type IV hypersensitivity. IG

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