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Sudden Death Due to Streptococcal Infection

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ABSTRACT: Sudden unexpected deaths form a large population of medical examiner caseloads. Presented are the clinical, pathologic, and virulence features of sudden death due to Group A beta-hemolytic streptococcus. Emphasis is placed on the importance of postmortem cultures. Case histories are included to illustrate the sometimes unusual presentation of this disease. Recent publicity has led to a heightened public awareness of this unusually virulent entity.

KEYWORDS: pathology and biology, death, streptococci, sudden death, postmortem cultures

Many sudden deaths investigated by a medical examiner are due to natural disease. Physicians are familiar with streptococcal pharyngitis and occasional poststreptococcal sequelae, including glomerulonephritis and rheumatic fever. Other more unusual presentations include erysipelas and cellulitis. All of these diseases are caused by Lancefield Group A streptococci, are easily treated with penicillin, and are rarely fatal.

Prior to the late 1980s, deaths due to acute Group A beta-hemolytic streptococcal infection were rarely identified. It was then noted that there were geographically discrete clusters of this disease occurring, with some fatalities. These clusters have been reported in California [*1*]; Denver, Colorado [*2*]; the Rocky Mountain region [*3*]; and the United Kingdom [*4*]. Most recently a cluster has occurred in the southwestern United States.

Those who have studied the epidemiology of this organism [*2,5*] have felt that the morbidity and mortality due to the Group A streptococcus have declined since the early 1900s. This decline occurred prior to the antibiotic era and may be due to decreased virulence of the organism itself [*5*]. In reality, the reasons for this decline are most probably multifactorial and also include environmental and host influences.

Presented are a series of sudden deaths due to Group A beta-hemolytic streptococcus. The presentations are unusual in that the interval between the onset of symptoms and death is very short, the clinical history does not readily bring to mind an infectious etiology, and the autopsy findings may be dramatic. The diagnosis of death due to these strains of Group A beta-hemolytic streptococcus rests almost entirely on postmortem cultures. These cases illustrate the unusual presentations of this disease, the rapid demise from seemingly minor symptoms, and the epidemiologic ramifications of the disease.

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Case No. 1

A 66-year-old white diabetic female presented to her family physician complaining of eye and facial swelling, which she thought was due to an allergic reaction to paint fumes. Physical examination showed mental confusion with severe facial edema and discoloration suggestive of subcutaneous hemorrhage. Within 8 h after her admission to the hospital, she was found unresponsive and pronounced dead.

The autopsy showed severe edema and subcutaneous blue-purple discoloration of the face, anterior neck, and chest in a geographic pattern. No abrasions or lacerations were present. There was focal sparing of the skin over the borders of the lower eyelids, upper lip, nose, and mid-chin (Fig. 1). The remainder of the skin surfaces showed no recent or remote trauma.

Internal examination confirmed severe subcutaneous edema and necrotic blue-purple areas of the head and neck. There was severe coronary artery disease with cardiac myonecrosis secondary to hypotension, chronic hepatic congestion, and nephrosclerosis.

Microscopic examination showed mononuclear cell infiltrates of the portal triads and a mild mononuclear cell infiltration of the corticomedullary junction of the adrenal gland. Intravascular and parenchymal aggregates of coccal microorganisms with focal mild surrounding tissue reaction were seen in the lung, liver, spleen, kidneys, and adrenal gland. Skin sections from the scalp and chest showed necrotic collagen and fat without inflammation, intravascular thrombosis, extravasated red cells, or microorganisms.

Postmortem cultures from the blood, lung tissue, and cisternal cerebrospinal fluid uniformly grew Group A beta-hemolytic streptococcus, M type 1, T type 1. Toxin types A and B were identified; Type C testing was not performed.

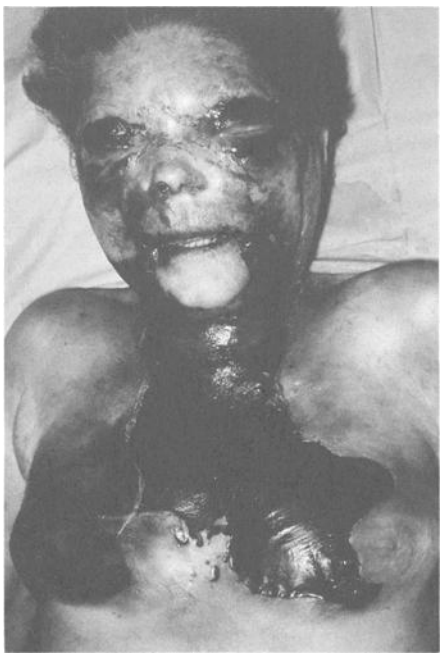

FIG. 1—*Extensive area of skin desquamation with surrounding blue-purple discoloration of the subcutaneous tissue in a patient dying of Streptococcal Toxic Shock-Like Syndrome. This illustrates one manner in which these patients may manifest the disease.*

Case No. 2

A 3-year-old Hispanic child was taken by the mother to a local clinic, where he was found to be unresponsive and cyanotic. Resuscitative efforts were unsuccessful. The child and other family members had been experiencing vague upper respiratory tract and abdominal symptoms. The child subsequently developed a rash, which the mother thought was measles.

Postmortem examination revealed patchy areas of skin desquamation and scattered punctate to linear crusted abrasions. Internal examination showed 200 cc of cloudy ascites, diffuse patchy bronchopneumonia, swollen tonsils, and systemic reactive lymphadenopathy.

Microscopic examination of the heart demonstrated scattered myofibril loss and vacuolization with an interstitial mononuclear and neutrophilic cell infiltrate. The liver sections were remarkable for periportal hepatocyte microvesicular vacuoles. The portal triads contained aggregates of eosinophils, neutrophils, and mononuclear cells, which extended through the parenchyma to adjacent portal triads. Mononuclear and neutrophilic infiltrates were present in the lung, adrenal gland, thyroid gland, pancreas, and tonsil. Although the cerebrospinal fluid cultures were positive, brain sections showed no cerebritis or meningitis. Postmortem cultures of the blood, lung tissue, and cisternal cerebrospinal fluid all grew Group A beta-hemolytic streptococcus. The viral cultures, including measles, were negative.

Case No. 3

A paramedic involved in the resuscitative efforts on the child described in Case 2 subsequently noted an abrasion on the back of his hand. Within 24 to 48 h he developed a cellulitis in the region of the abrasion and became hypotensive. Wound cultures were positive for Group A beta-hemolytic streptococcus. He was treated with intravenous penicillin for 2 days and discharged on oral penicillin. Within 24 to 48 h he again became symptomatic, requiring a second hospital admission with intravenous penicillin and subsequent outpatient treatment.

The streptococcal M and T types and exotoxins were identical for the child and the paramedic; M type 2, T type 2/8/25/I-19, toxins A, B, and C were identified.

Case No. 4

A 53-year-old Indian female presented to a local hospital with complaints of nausea, vomiting, dizziness, intermittent fever, and mild upper respiratory complaints. She had a medical history of diabetes mellitus and urinary tract infections. During the hospital admission examination, she suddenly became unresponsive and died.

Although the body was cooled and an external postmortem examination was completed within 12 h of death, decomposition changes suggestive of sepsis were present, which included venous marbling with skin slippage and blisters over the forearms and lower extremities. Internal examination was not performed at the family's request. Premortem blood cultures were positive for Group A beta-hemolytic streptococcus, M type 1, T type 1; Toxin B was identified.

Discussion

These cases demonstrate the varied presentations of this ubiquitous disease. The use of postmortem cultures made the diagnoses straightforward; however, without them, these findings and histories could have been easily misinterpreted. The differential di-

agnoses for these cases include blunt-force trauma, burn injury, allergic reaction, poisoning, and infection.

The determination of the cause of sudden death includes an algorithm of the patient history, external and gross examination, microscopic examination, and toxicological analysis. In selected cases, the use of postmortem cultures is imperative in determining the accurate cause of death and should be considered. Although postmortem cultures are recognized as being helpful in establishing the cause of death in infants and children, these cases illustrate their importance in adults.

The most likely mechanism of death in fulminant Group A beta-hemolytic streptococcal infection is septic shock. The differential diagnosis of septic shock includes staphylococcal toxic shock syndrome, clostridial or diphtheria toxins, meningococcal sepsis, and gram-negative bacteremia. The most commonly implicated gram-negative organisms are *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Pseudomonas* species, and *Bacteroides* species. Classically, these disease processes are associated with characteristic historical presentations. Clostridial disease is associated with trauma or food ingestion; diphtheria presents with upper-respiratory tract symptoms and pseudomembrane formation; gram-negative bacteremia is associated with urinary or intestinal tract disease.

Of those listed, the two organisms that remain in the differential diagnosis are the meningococcus and *Staphylococcus aureus*. With the aid of the history, gross findings, and cultures, pathologists can distinguish these two entities from streptococcus.

Meningococcus affects children and those in crowded conditions, such as military recruits or college students. The organism is present in the nasopharynx in the carrier state. These patients develop a petechial rash with subsequent bacteremia and meningitis. Although they are not pathognomonic of the meningococcus, we may see hemorrhagic adrenals, as in Waterhouse-Friderichsen syndrome and gross meningitis. Favored postmortem culture sites include the blood and cerebrospinal fluid.

Toxic shock syndrome is associated with *Staphylococcus aureus* and tampon use. It affects previously healthy menstruating young women. They experience sudden onset of high fever, rash, desquamation of the palms and soles, vomiting or diarrhea, renal insufficiency, and elevated liver enzymes. Symptoms begin during the menses. The disease is mediated by exotoxin C/enterotoxin F. Favored culture sites are the vagina and cervix. One report [*6*] cites positive vaginal cultures in 13 of 19 cases, cervix cultures in 8 of 12, blood cultures in 2 of 27, and cerebrospinal fluid cultures in 0 of 12 cases. Gross and microscopic findings include ulceration, inflammation, or congestion of the cervix or vagina; congestion, edema, or focal hyaline membranes of the lung; portal triad inflammation; microvesicular fatty changes of the liver; and acute tubular necrosis of the kidney [*7*]. The heart, adrenals, and pancreas are normal.

Cases of streptococcal shock have the basic common denominator of acute onset of life-threatening shock. Hence, the pseudonym "toxic shock-like syndrome." There is often a history of minor, nonspecific upper respiratory tract or abdominal complaints over the two to three days prior to death. Another presentation is one of cellulitis, which may or may not have an associated laceration/abrasion in that region. The cellulitis can be described as an area of edema with subcutaneous blue-red discoloration in an irregular pattern with areas of sparing.

There are no pathognomonic features of the disease, only a history of minor complaints followed by death. Gross examination may show minor bronchopneumonia, hemorrhagic adrenals, ascites, and findings secondary to hypotension, but nothing specific to the disease. The brain and meninges are normal.

The literature cites few examples of the microscopic features of this disease entity. Those described [*1,8*] include mild lymphohistiocytic inflammation and wavy myofibrils in the heart and microvesicular and macrovesicular fat in the liver without portal inflammation. Organs of interest to examine microscopically include the heart, lungs, adrenal, and liver. Brain sections are helpful to exclude meningitis.

Without postmortem cultures, this diagnosis can and will be easily missed or misinterpreted. As forensic pathologists, we may resist performing them; we often find them difficult to perform, and many times the culture results are less than satisfying. The selective sampling of heart blood immediately after opening the pericardium, lung tissue after opening the chest cavity, and cisternal cerebrospinal fluid are adequate for the diagnosis. Positive results in multiple sites ease the interpretation and minimize problems that may arise with a contaminated specimen.

The cultures are also very important from an epidemiologic standpoint. Cases 2 and 3 are very good examples of this. The cultures not only answered the question of whether the paramedic had acquired the same disease as the child, but, my means of M and T antigen and toxin typing, these cultures were shown to be concordant strains. Such findings may have implications for work-related compensation. The cultures also allowed the other family members to be followed closely and to be treated expeditiously.

To understand why the seemingly innocuous streptococcus should behave in this way, it is important to discuss the microbiologic features of the organism, including the M and T antigen typing and exotoxins.

The changing characteristics of the organism itself may account for case clustering and its virulent nature. The streptococcus is characterized by a cell wall protein called M protein. These are specific amino acids which confer uniqueness to that specific strain and the development of M-type specific immunity in the host. The M protein has classically been related to the virulence of the streptococcus through resistance to phagocytosis. No single specific M protein has been identified as causing recent outbreaks. Comparison of the different reports where there have been toxic shock-like manifestations of the disease shows an increased incidence of M protein types 1 and 3. This incidence varies between 60 and 100% [*2,3,9*]. If a host is exposed to a new serotype, that is, one to which he has not previously developed immunity, he is susceptible to developing disease. However, the presence alone of the organism does not indicate disease: its presence must be correlated with the patient's clinical appearance. Subsequent throat cultures of family members of the child in Case 2 were positive for Group A beta-hemolytic streptococcus, yet only the child manifested severe symptoms.

Some M antigens are unable to be identified and are called nontypeable. Theories for this include the absence of an M antigen, a slight modification of the M antigen so that it is no longer reactive with the known typing sera, or an entirely new antigen for which typing sera have not been developed [*10*]. The expression of the antigens may be influenced by how many times the organism has been subcultured in the laboratory [*11*].

Characteristic T antigens are also a feature of the streptococcus. They are similar to M antigens in that they are proteins in the cell wall which can be used for epidemiologic purposes. However, they differ from M antigens in that they are less specific and are not related to virulence. Typically, low-numbered M antigens have the same T antigens. Their usefulness is related to their greater ease of identification, which may aid the laboratory in identifying the correct M antigen. In doing so, T antigens may provide another parameter which can be used in comparing the two organisms.

Also characteristic of the Group A streptococcus is the production of protein exotoxins A, B, and C. In the United States, until recently, strains producing toxin A have been infrequently identified [*12*]. Historically, they are related to the scarlet-fever-producing organisms of the early 1900s [*13*]. The interesting characteristic of streptococcal toxin A is the homology of its protein sequence with that of *Staphylococcus aureus* exotoxin B, which also produces symptoms of nonmenstrual toxic shock [*14*]. Eighty percent of the clustered cases reported from the Rocky Mountain region demonstrated production of exotoxin A [*9*]. Toxins may be the mediator for multiorgan system failure and rapid progression of the disease.

The streptococcus may be capable of undergoing antigenic drift similar to that in influenza A [*15*]. The particular virulent strains of streptococcus associated with these

outbreaks are thought not to have surfaced since the scarlet fever epidemics of the early 1900s. Most people probably do not have immunity to these streptococci. Although not everyone appears to be equally affected by contracting the organism, its presence is being felt. We will undoubtedly be encountering and identifying more deaths in the future.

Summary

These virulent streptococcal strains are becoming more prevalent throughout the United States and probably throughout the world. Whether this is due to increased virulence of the organism, decreased resistance of the host, or the production of more powerful exotoxins is unclear.

The clinical and postmortem manifestations of the disease are widely varied. While toxicology and microscopic examination aid only by excluding other causes of sudden unexpected death, the external and gross manifestations, in conjunction with the history, will provide clues for suspecting the disease and for performing cultures.

As the physicians ultimately responsible for identifying the cause of unexpected death, forensic pathologists need to be aware of this entity and include it in the differential diagnosis of sudden, unexpected death. Postmortem cultures are imperative for accurate diagnosis and potentially life-saving epidemiological investigation.

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