Viral myocarditis
Clinico-Pathological aspect with literature review

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INTRODUCTION

Myocarditis is a primary or secondary myocarditis which is prevailing in the world may be caused by various types of inflammation, toxic or hypersensitivity states. The most commonly encountered causative agents of the myocarditis are bacterial, rickettsial, viral, protozoal, parasitic, fungal, spirochetal organisms, chemical reagents, drugs, alcohols, allergic condition and radiation. Out of viral myocarditis, the coxsackie virus has been regarded as the most commonly encountered causative factors of human viral myocarditis. The isolation and characterization of the coxsackie virus had been made approximately 3 decades ago. As previously mentioned the coxsackie virus has been classified as one of the enterovirus and possessing two distinct groups which distinguished as viral A and B as seen in Table 1. The group A is consisting of 24 subtypes which causes in mice a diffuse skeletal myositis and flaccid paralysis, while group B with 6 subtypes, causing myocarditis and spastic paralysis. The coxsackie B virus is clinically stated as most cardiotoxic. In man, the infection due to this coxsackie virus is frequently encountered and the group A virus causes a "Flu-like" syndromes, foot and mouth disease like syndrome, herpangina, febrile respiratory poliomyelitis-like disease, and a variety of cutaneous eruption. The group B virus also causes "Flu-like" illness, together with Bolbolm like disease, glandular fever, or lymphadenitis, orchitis, pancreatitis, encephalitis and myocarditis as well as pericarditis. The group B also produces intrauterine infection, which seems sometimes lethal to the neonatal infant. The association between neonatal coxsackie infection and epidemic pleurodynia or Bolbolm disease in adults is confirmed by the isolation of coxsackie virus from stool, cerebrospinal fluid, pleural fluid of mother who was affected with pleurodynia, and by postpartum elevated titration of antibody titer in the serum. The true incidence of acute

Table 1 Virus associated with myocarditis in human

RNA.-
1.-Picornavirus : Coxsackie A  Coxsackie B Echo Polio.
2.-Orthomyxovirus : Influenza A Influenza B A+B.
3.-Paramyxovirus : Rubeola Mumps.

DNA.-
1.-Poxvirus : Variola Vaccinia,
2.-Herpesvirus : Varicela zoster Cytomegalo Epstein Barr.
3.-Adenovirus : Adeno.

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viral disease in general population is a matter of much controversy, because of the difficulty of establishing final diagnosis. However, the frequency of this detection in the literature are reported as autopsy report as varies between 2.9 and 9.2%. This disease may attack at any age group, but it has been noted that neonatal infant and adult group are most commonly affected.

1. Clinical manifestations

Most of information concerning the clinical manifestations of viral myocarditis is based on the observations of patient who are infected with coxsackie B virus. The clinical heart disease due to this virus is very characteristic of myocarditis as well as pericarditis. The diagnosis is often clinically missed and the diagnosis entity is often confusing. The only confirmation that can be made by the electrocardiogram is the abnormality of the conduction system or the changes which suggest acute myocardial infarction (Fig. 1). Acute disease in neonatal infants is most frequently seen at 5 to 10 days of age, approximately after the incubation period of the 2~8 days.

In the early stages of infection, pyrexia, tachycardia, and inactivity of the muscular contraction are noted. These changes may be followed by tachypnea, cyanosis and rapidly progressive circulatory collapse. In adolescent and adult stages, initial symptoms are often of an upper respiratory infection, such as influenza or gastrointestinal distress. Acute heart disease is usually not detected until about a week to 10 days later and shows symptoms consistent with the pericarditis, coronary artery occlusion or progressive heart failure. Miscellaneous signs and symptoms such as fever, myalgia and headache are frequently seen. The cardiac involvement shows persistent tachycardia, gallop rhythm or friction rub due to concomitant pericarditis, and other certain irregular heart beats such as atrial fibrilation or flutter. Atrial, nodal ventricular tachycardia and cardiomegaly which is resulted from the ventricular dilatation or pericardial effusion are seen. Accelerated erythrocyte sedimentation rate, serum glutamic oxalacetic transaminase, creatinine phosphokinase, lactic dehydrogenase elevation, and increase of alpha and beta immunoglobulin will frequently follow. Arrhythmias or congestive heart failure is also a very common feature. Chronic myocarditis is known to occur in parasitic disease in man and has been seen experimentally

![ECG shows typical atrio-ventricular block in V1](image)

Fig. 1 ECG shows typical atrio-ventricular block in V1.
after inoculation of coxsackie virus B-3. Clinically the viral myocarditis also can be classified into subacute, chronic and recurrent varieties. Subacute cases have been reported in adult patients who cardio-respiratory symptoms have been continued during over one month. Coxsackie B-virus was isolated from a myocardial biopsy obtained during the last week of life and neutralizing antibody titer of 1/64 was detected in the post-mortem serum in this reported case. Chronic myocarditis is mentioned when the patient reported has been certainly diagnosed as viral myocarditis with an evolution period of one year. Subacute, chronic and recurrent types show evidence of the inflammation and myocardial necrosis which lasts in man for a period of two years and eventually proves to be fatal.

2. Pathology

As previously mentioned the most commonly encountered viral myocarditis in infant and adult is coxsackie B virus group. After 2~5 days of infection, the characteristic findings are left ventricular dilatation. However heart weight is not increased at this stage. Grossly the dilatation of left and right ventricles are frequently observed. The myocardium is flabby, pale, mottled dark red, and yellow gray in color, particularly along the left ventricular wall and interventricular septum. Subendocardial hemorrhages may be seen at any stage of the disease, while myocardial intramural hemorrhage usually takes place in this stage. Epicardial or myocardial petechiae are associated with pericarditis, The epicardium is covered with fibrin and effusion. Microscopically, the necrosis of myofibers and inflammatory cell response are the dominant findings. Necrosis of myofibers is either patchy or diffuse and may occur at any site, although left ventricular involvement is most commonly described. Necrotic myofibers have been observed at 2 days after the onset of illness. At the initial stage the inflammatory infiltration are composed of polymorphonuclear leukocytes. By the fifth day, the myofiber destruction is observed, and the infiltration of the mononuclear inflammatory cells is also noted. Histiocytes, lymphocytes, and plasma cells strikingly increase at the 9th day. Numerous myofibers have undergone disintegration, leaving scattered masses of the chromatin. By 11th days, the necrotic areas are clearly demarcated from the surrounding tissues. Calcification of partially necrotic myocardial cells is observed after the 9th days. Then the activation of the fibroblast and the replacement of the myofibers with granulation tissue are noted.

Although there are exceptions, the histologic findings after infection with many viruses are identical. In the early stage of the disease, scattered hypereosinophilic myofiber, widespread edema, and occasional inflammatory cells are noted (Fig. 2).

Later, myofibers exhibit loss of the striations, dumoing of the cytoplasm. The foci of the partial necrosis myofibers are usually surrounded by mononuclear cells, such as lymphocytes, plasma cell and macrophages. The specific predilection of the viral infection such as the Purkinje cell is described and offers much related to the causative mechanism. The exact mechanism should await further confirmation in future, however, abundant presence of glycogen particles or enzymes, related to the intermediate metabolism such as the choline esterase in the cells may facilitate the causation of infections process in these specific sites. The ultrastructural myocardial changes produced by viruses have been studied
since the electron microscope has opened an extensive new field in cardiological investigation. The ultrastructural changes in the myocardium induced with infection in experimental animals have been correlated with human ultrastructural changes in patients died of viral myocarditis. The earliest alterations occur in the mitochondria which reveals amorphous material accumulation in intra-cristal space and then sarcomeres begin to assume a more fuzzy appearance, and also small granules could be well distinguished from glycogen particles and ribosomes are noted and this could represent virus-like particles. The fragments usually tended to be most numerous near the sarcolemma. The sarcoplasmic reticulum show dilatation of the cisterna and associated large vesicles. The cytoplasmic pseudopodal processes are often observed. As the lesions become more relapsed, severe myocyte degeneration is noted and the entire architecture is obliterated. Autophagic vacuoles and vesicles also increase in the cytoplasm of myocardial cells. The localization of the crystals, resembling viral inclusion is coincidental with the stain property of immunofluorescent of antibody technic to coxsackie B antigen in myocardium (Fig. 3).

3. Diagnosis

Isolation and identification of the virus from the myocardium or pericardial fluid is extremely helpful in confirming the entiology of myocarditis. The repeated virological study also substantiate the diagnosis. The most common approach is to detect infectious virus from these specimens by inoculation of cultured cells, embryonated avian eggs, or susceptible animals. As an alternative to viral isolation, tissues or fluids may be examined directly for viruses or pathognomonic changes by means of the light and electron microscopic technics.
Viral antigen can also be detected in a variety of tissue by use of both, direct and indirect immunofluorescent techniques. These methods are versatile for the rapid diagnosis of viral infection and is applicable to both antemortem and postmortem tissues and fluids. However, the ability of the test results depends on the proper preparation of specimens, the quality of the reagents used, the skill of the laboratory personnel and the appropriate use of the equipment. Particular attention should be paid to the eliminating the nonspecific fluorescent distribution in the myocardium. This difficulty is further augmented by the fact that some viruses, for example, picornaviruses are not routinely studied in the laboratory by these techniques because of lack of the specificity and sensitivity of the method and unavailability of good reagents for the study. Moreover, some investigators have found that specific immunofluorescence can not be detected even when high titer of the picornavirus are present in the myocardium. Serologic evaluations are sometimes the first choice for the physician who suspects the patient has been infected with coxsackie virus. Most of the viral infections, the diagnosis is established by demonstration of a fourfold rise in specific antibody titers in acute and convalescent serum specimens. The ordinarily serum antibody is not detected until a few days to one week after the onset of clinical disease.

In conclusion, the importance of the viral myocarditis in Japan is fully augmented with literature review in this communication.

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REFERENCES


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