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Euro Virology 2018: Impact of pathology in study of viral infections- Vsevolod A Zinserling- Saint Petersburg University

Vsevolod A Zinserling

Department of Pathology Institute of Experimental Medicine V.A. Almazov Research Center, Saint-Petersburg University, Russia

According to expert estimations, from 30 to 50 million cases of infectious diseases occur in the world, the economic damage from which is not currently calculated. COVID19 pandemia is the most impressive example. The economic damage from the coronavirus pandemic currently cannot be calculated exactly, but surely is enormous.

We are sure that the true significance of infections is much greater than commonly accepted previously. This, of course, is associated with a whole range of factors, among which the failure in many cases to perform qualified autopsy examinations or to underestimate their data is important. It should be noted that, despite a significant number of modern studies devoted to certain aspects, primarily the molecular biology of a number of pathogens, epidemiology, diagnosis and treatment of the most relevant infectious diseases, some aspects remain as if in the "shadow". This primarily relates to issues of pathology. The literature does not provide a complete morphological characteristic of any of the newly discovered infections.

It is obvious that a fruitful study and diagnosis of infectious pathology should be comprehensive and must include an analysis of structural changes. Summarizing long-term experience in studying the pathology of infections in our scientific school, it seems appropriate to formulate the following requirements for the morphological study of the infectious process on autopsy and biopsy materials: 1) identification of pathogens and their components in tissues (due to detection of viral antigen, NA sequence or typical inclusions); 2) a broad comparison of morphological data with clinical and laboratory; 3) differentiated assessment of changes caused by individual pathogens; 4) assessment of the characteristics of tissue reactions in different etiology and the form of the infectious process; 5) the widest use of nosological experimental models of infections in order to clarify patho- and morphogenesis and evaluate the effectiveness of therapy; 6) the study of interactions between various pathogens in mixed infections with each other and with the host; 7) the study of peculiarities of infectious processes in different organs and tissues; 8) determination of the immediate causes of death in infections. The listed principles are well known to many experts, but they have been rarely summarized.

In Saint-Petersburg/ Leningrad (Russia, former Soviet Union) pathology of viral infections (influenza and other respiratory viral infections, herpes, hepatitis B and C, HIV etc) has been studied by Alexander V. Zinserling (Tsinzerling) (1923-1995), his collaborators and pupils since the top of 60th . I present here some most important issues on example of influenza.

The most significant data received at that time was demonstration of typical cell changes, called "influenza cells". Cytoplasm enlarged being at early stages of the disease basophilic, afterward parallel with virus disappearance pale stained and showing signs of degeneration. Intracytoplasm fuchsinofilic inclusions were considered as very typical, although not specific, for influenza, representing the necrotic foci surrounded by membrane. Appearing as small dots in the perinuclear zones they grew in size and were transferred at the periphery being expelled afterwards. Such transformations were observed in ciliated epithelial cells of trachea and bronchi, alveolocytes and lung macrophages. As exception such inclusions were noted also in smears from meninges and placenta. In infants and small children basing upon clinical, virological data and immunofluorescent microscopy generalized infection was proved in many cases with developing of brain, liver, kidney, intestine, adrenal lesions partly with appearance of "influenza cells". In adults the majority of lethal cases were explained by bacterial, at that time usually staphylococcal, superinfection leading to destructive pneumonias. Mucous layer in larynx, trachea and bronchi was swollen with mixed infiltration and desquamation of epithelium. Viral antigen could also be detected in capillary endothelium. Described changes were found in all cases of influenza due to viruses H3N2 and B, regardless its clinical manifestation. In cases with expressed clinical symptoms were observed lung edemas, plethora of vessels with hemorrhagic foci. Neutrophilic infiltration was considered as a hallmark of bacterial superinfection. Indeed, in majority of cases of focal pneumonias virus-bacterial associations have been found. Bacterial pneumonia can be both community and hospital acquired.

Later on, the progress of clinical and medicine resulted in critical decrease of lethal outcomes thanks to influenza. Situation changed with appearance of the new "swine" strain of virus.

Pathological features and disease severity depend on patient general state and susceptibility, as well as the virus type in question. So, called H1N1 avian influenza virus is considered to be the most dangerous, causing generalized infection with high lethality. Seasonal H3N2 and H1N1 influenza viruses that are circulating in recent years tend to cause primarily localized respiratory tract infection, although extrapulmonary lesions may occur in severe cases. New H1N1 influenza virus also causes mainly localized infection, but in most autopsies signs of generalization can be found. Also, it should be noted that bacterial co-infections are relatively rare.

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Our experience based upon about thousand observations in the period 1977-2019 allows us to make several not widely known statements.

Clinical course of influenza may differ and sometimes, usually in intraepidemic periods, the disease may manifest with moderate symptoms usual for all acute respiratory infections of various viral etiology (rhinitis, cough etc).

Our data allow to verify the existence of previously described in experiment chronic sorts of influenza without distinct clinical symptoms, having the ability to be activated in unfavorable for the patient situation, superinfection by other pathogens first of all. Persistence of viral antigens in lung macrophages without signs of inflammation has been proved in our study with the help of immunohistochemistry. One can submit that this phenomenon has to be studied specially and can be considered in relation to survival of "not actual" viral strains. Once we had the opportunity to detect such strain in plexus chorioideus of 4,5 mth girl.

It is widely accepted and properly investigated that each one types, and antigenic variants of influenza virus have tropism to ciliated epithelial cells of trachea and bronchi of various caliber. In single publications it has been demonstrated that alveolocytes, lung macrophages and endothelial cells can be considered can be considered as targets for virus as well. In accordance with our experience virus exposed cells are submitted to typical transformation which may differ thanks to properties of virus strain. During the infection caused by virus with short replicative period (H3N2 as example) one can observe during the first 3 days of the infection the cells with the enlarged slightly basophilic cytoplasm ("influenza cells" of A. Zinserling) (fig.1). Such changes we explain by active viral replication. Later on (5-7th day of the disease) the cells are desquamated and undergo necrotic changes, which are hallmarked by cytoplasm becoming pale with indistinct cell borders. In the infection due to strains with prolonged virus replication in lungs (H1N1 California first of all) one can assume that virus-cell interactions undergo important modifications and the infected cells instead of dying express proliferative changes. In our experience they can become binucleated, considerably enlarged, multinucleate or even undergo squamous cell metaplasia. It is evident that the fine mechanisms of such only recently described phenomenon needs the further study.

In many lethal cases thanks to influenza we affect mixed infection. Most evident variant of its development is bacterial superinfection in course of influenza leading to defect of defense mechanisms of respiratory tract due to desquamation of ciliated cells. Later on, virus-bacterial pneumonia develops playing an important role in clinical manifestations and tanatogenesis in lethal cases. Bacterial pneumonias are focal, usually confluent, frequently with signs of tissue destruction. The etiology of such bacterial superinfection can differ, in certain periods of your time with prevalence of staphylococci, but in majority of cases stays undetermined either clinically nor at the autopsy. Interestingly that during the lethal outcomes in 2009-11 with leading role in pathogenesis of diffuse alveolar damage (DAAD) the expression of neutrophilic infiltration usually explained by bacterial component was rather modest. Certainly, this fact can partly be explained as result of efficacy antibiotic treatment, but the same tendency was noted also in the patient without it.

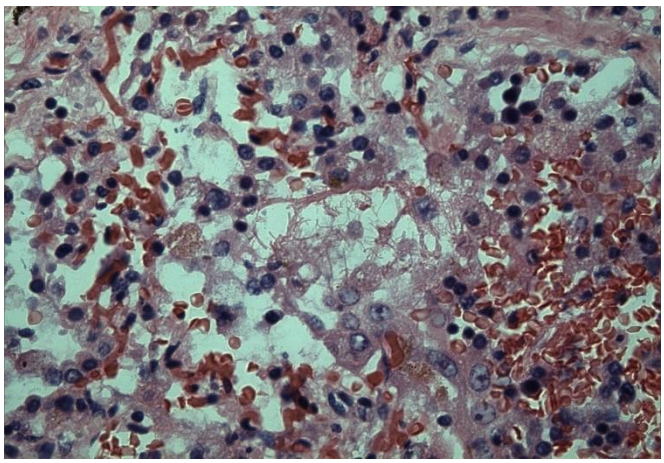

Fig1. Lungs in lethal H1N1 influenza, first type virus-affected ("influenza") cells with prominent hyperemia and dystelectases, H&E, x400

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