reports

Editorial

A Memorial Paper on Professor Takatsuki, Who Devoted Himself to the Case Report

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This is a memorial paper for Prof. Takatsuki, who discovered three distinct clinical diseases. Heavy chain disease was reported in 1964, and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) were reported in 1992. He also reported adult T cell leukemia in 1976. His important discoveries were based on keen clinical observations and the analysis of clinical materials. The discovery of adult T cell leukemia (ATL) and the independent isolation of human T cell leukemia virus type 1 (HTLV-1) has established a direct causal relationship between ATL and HITV-1. The studies on host–pathogen relationships in ATL led to the expansion of the research in emerging and disaster-related infectious diseases

Prof. Kiyoshi Takatsuki passed away on 23 May 2021, at 90 years of age in Kyoto. He graduated from Kyoto University in 1954. He worked as a physician and demonstrated excellent talent for medical observations of the patients. He worked on diseases associated with plasma cell dyscrasia and worked at Columbia University with Professor E.F. Osserman. They found four cases: (1) proliferation of the cells of the plasmacytic and reticulum cell series, associated with the clinical pattern of a malignant lymphoma; (2) excessive production of polypeptides which are related to the H (heavy) polypeptide chains of the 7S gamma$_2$ globulins (designated $H_{\gamma 2}$-chains); and (3) a decrease in the synthesis of normal gamma globulins. These diseases were named as heavy chain diseases as a distinct clinical entity [1,2].

After returning to Japan as a lecturer at Kyoto University, he found a case of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome associated with focal spinal amyloidosis [3] he also summarized 109 cases of POEMS in Japan and reported that this syndrome shows (1) polyneuropathy with increased protein levels in the cerebrospinal fluid and sometimes papilledema; (2) endocrinological symptoms, including skin pigmentation, sclerosis, hypertrichosis, gynecomastia, impotence, amenorrhea, decreased glucose tolerance, edema, pleural effusion and ascites; (3) hepatomegaly, splenomegaly and lymphadenopathy; (4) polycythemia, leukocytosis and thrombocytosis; (5) osteosclerotic changes; and (6) plasma cell dyscrasia [4].

In 1976, he reported that adult T cell leukemia (ATL) shares some features with Sezary syndrome but is distinct. The disease is characterized by (1) adult onset; (2) ATL cells showing characteristic morphologic features, especially deep indented nuclei (Figure 1); (3) frequent associations of skin involvement (Figure 2), lymphadenopathy and hepatosplenomegaly; (4) a high leukemic cell count in the peripheral blood without anemia and with only modest involvement of the bone marrow; (5) hypercalcemia; and (6) a geographic clustering of cases. The most striking feature of ATL, and the original basis of its proposal as a distinct clinical entity, was the clustering of birthplaces of patients in the southwestern part of Japan [5].

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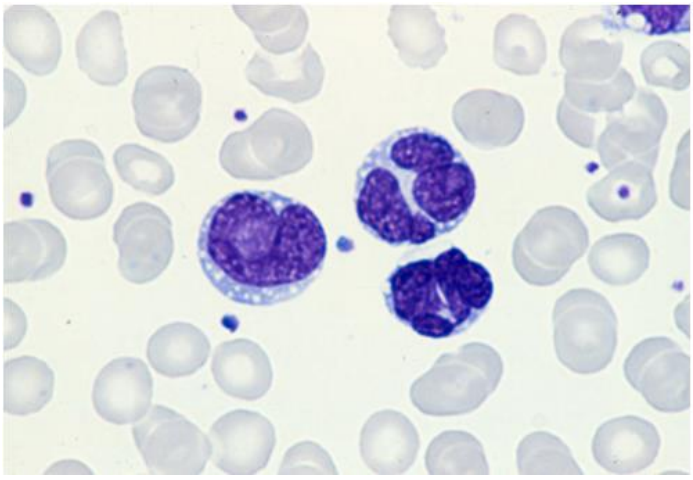

Figure 1. May–Giemsa staining of ATL cells (×400). ATL cells with a kidney shape (left), lobulated (center) nuclei and a normal polymorphonucerar cell (lower right).

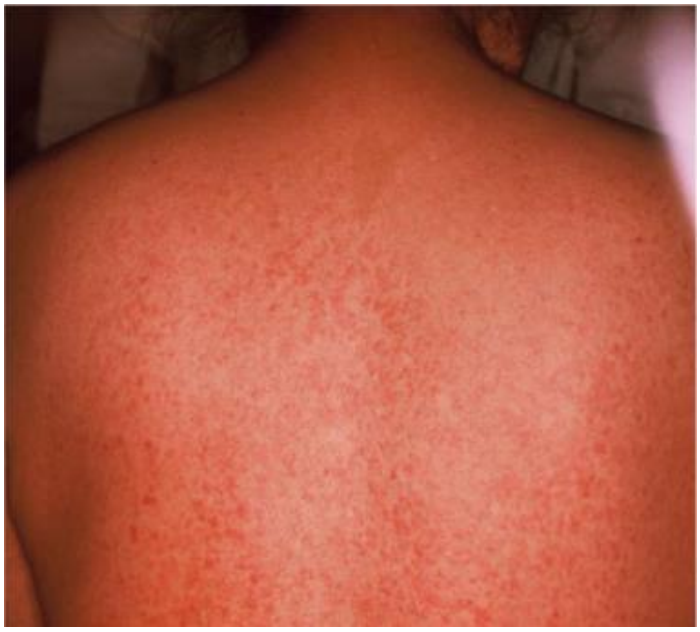

Figure 2. Papular rash in a patient with acute ATL. Various skin lesions including tumors are observed in ATL patients.

In 1980, the isolation of human T-cell leukemia virus type I (HTLV-1) from a patient with cutaneous lymphoma (mycosis fungoides) [6] was reported by Dr. Gallo's group at the National Cancer Institute in the United States. They later noticed the clinical similarities of mycosis fungoides and ATL and subsequently showed that anti-HTLV-1 antibody is prevalent in patients with ATL [7]. The successive collaboration revealed that southwestern Japan was the most endemic area in the world and HTLV-1 was recognized as the first human retrovirus that causes cancer [8,9]. The finding facilitates the discovery of acquired immune deficiency syndrome and human immunodeficiency virus type 1 [10]. These diseases have become a research model of pathogens and their host response to them, and the stimulated research has spread to the study of various infectious diseases. For example, the discovery of osetopontin as a prognostic factor in ATL [11] led to the study of osteopontin in tropical and disaster-related infectious diseases, such as dengue virus infection [12,13].

Prof. Takatsuki said that he was interested in ATL patients because their face had the characteristics of people of southern descent rather than those of western Japan.

Having been involved in the discovery of three diseases, I have to admit that he had a special power of observation. Of course, the case report was the beginning of these discoveries as written in the editorial of this journal [14]. However, it is not possible to establish a new disease solely by clinical observation. He clarified how to detect heavy chain diseases using papain-digested products [1]. Raising anti-T cell antibodies also helped to establish ATL [15].

He also extended clinical studies which have opened up new research areas. The characterization of ATL cells as CD4+ and CD25+ with suppressive activity contributed to the discovery of regulatory T cells [16]. The findings of the synthesis of chemokines by ATL cells also led to the development of anti-chemokine receptor therapy against ATL [17].

He was awarded the Hammer prize in 1985 and selected as a person of merit of culture in Japan in 1995. The Hammer prize was given to Drs. Gallo, Profs. Takatsuki, Hinuma and Miyoshi. Prof. Hinuma contributed to the detection of antibodies in serum of ATL patients against ATL-derived cell line, MT-1, which was established by Prof. Miyoshi [18,19]. The independent work of these scientists and subsequent collaboration established a direct causal relationship between ATL and HTLV-1. This breakthrough was made possible because ATL was clinically established by Prof. Takatsuki (Figure 3).

Figure 3. Prof. Takatsuki (center) and his wife, and Princess Takamatsu (left), at Princess Takamatsu cancer research fund prize (1983).

Conflicts of Interest: The author declares no conflict of interest.

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