Results generated through the Grants-in-Aid for Scientific Research Program No.2 (Mar.2012)

Story about Discovery of Adult T-cell Leukemia and HTLV (Part II)

2. Prevention and Treatment of Disease

Leukemia is not the only disease caused by HTLV. Hiroaki Igata of the Kagoshima University Department of Internal Medicine discovered that in this region of Japan, the blood and spinal fluid of patients afflicted with spastic spinal paralysis, a neural disease, contained HTLV antibodies. From its association with the HTLV virus, this disease came to be known as HAM (HTLV-I-associated myelopathy). It has been found that the tropical spastic paraparesis often seen in Middle and South America, India and Africa are also HAM, caused by HTLV infection. Furthermore, the virus is responsible for some diseases of the eye. It causes uveitis, an inflammation of the interior of the eye, with symptoms such as blurred vision and decline in vision.

In Japan, the overwhelming majority of HTLV carriers are found in the Kyushu and Shikoku regions of southern Japan, to a lesser extent in the Sanriku region of northern Japan, and among the Ainu peoples (Fig. 1). However, for reasons unknown it is virtually nonexistent in Korea and China. Kazuo Tajima of the Aichi Cancer Center collected samples from around the world to test for viral genes. As a result, it was found that besides Japan, the virus is most prevalent in the countries of Africa and Central and South America (Fig. 2). The total number of HTLV carriers around the world is estimated to be about ten to twenty million. The DNA of this virus has even been found in a mummy excavated from the Andean Highlands, dated to about 1500 years ago (Fig. 3). Moreover, its genome sequence was similar to the virus found among Ainu and Japanese. Tajima speculates that this virus originated in Africa and spread by way of Asia, ultimately reaching Central and South America. But the fact that HTLV has existed for so long in the history of mankind is not due to heredity. It is because of the vertical pathway of infection in which the virus has been passed on from mother to child.

HTLV is passed from person to person through T lymphocyte cells infected with the virus. Transmission has occurred through the following three routes:

- From mother to child (breast milk contains T-cells)
- From male to female (sperm contains T-cells)
- Through blood transfusion
  (eliminated when screening for the virus was established in 1986)

In 1984, Shigeo Hino of Nagasaki University established that the disease was transmitted from mother to child through breast milk. It was found that 22% of the children born to mothers who carried HTLV were infected. This virus had long been transmitted from mother to child. If breast milk was the only principal route of infection, transmission could be prevented by switching to bottle-feeding. In Nagasaki Prefecture, Hino supervised the guidance of carrier mothers to stop breastfeeding. As a result, infection from mother to child was reduced to 3%.

Since this disease was concentrated in the Kyushu region of Japan, officials felt no need to take nationwide courses of action and were even optimistic that the disease itself would eventually disappear with the decline of breastfeeding (1990 Ministry of Health report). But the number of people believed to carry the virus did not drop as expected, remaining at about 1.1 million people (about 1% of the population of the region) for the last 20 years. Moreover, with the increasing concentration of city populations, the disease began to emerge in large numbers in the Kinki and Tokyo areas, necessitating the implementation of nationwide measures.

About 1,200 cases of adult T-cell leukemia occur annually in people who carry the HTLV virus. The majority of patients die within one year after onset. Of the many types of leukemia, adult T-cell is one of the most dreaded. Actually, it is more accurate to say, "was the most dreaded." Recently there have been cases in which the disease has been successfully treated. Shiro Asano (former governor of Miyagi Prefecture) was able to recover from the disease after receiving bone marrow transplantations, to the extent of making television appearances. Ryuzo Ueda of Nagoya City University developed the CCR4 antibody, which is effective in treating adult T-cell leukemia. CCR4 (CC Chemokine receptor 4) is specific to adult T-cell leukemia, and treatment using the CCR4 antibody succeeded in inducing full recovery or remission in 50% of those afflicted. The CCR4 antibody is currently in phase III of testing needed for approval as a new drug (related article in *Kakenhi News* Vol. 114, 2011). And recently, a research team led by Shimon Sakaguchi of Osaka University World Premier International Research Center Immunology Frontier Research Center (WPI-IFReC) has been engaged in vaccine therapy targeting proteins specific to cells of this type of leukemia.

The case of former governor Asano became the catalyst for the government to undertake measures against adult T-cell leukemia, which had been all but forgotten until then. The cabinet under then-prime minister Kan set up the Task Force Team for HTLV-1 in October 2010 and drew up their plans for comprehensive measures in December of the same year. In 2011, screening for HTLV was added to checkups for pregnant women to prevent transmission from mother to child.

Following the discovery of adult T-cell leukemia in 1973, we have made steady progress in combating the disease: identification of its pathogen virus, taking steps to prevent its transmission, development of a curative drug, and today, implementation of comprehensive measures. The discovery of HTLV, the first retrovirus known to exist in humans, has paved the way for research on HIV. It can be said that this special research project has produced results that mark a milestone in the field.

Cancer research in Japan began in 1966 with support provided for over 40 years through the programs Cancer Special Research, Cancer Priority Area Research, and Scientific Research on Priority Areas. Since 2010, these programs have been absorbed into the Grant-In-Aid for Scientific Research on Innovative Areas. Looking back, cancer studies have been made possible through progress in the field of genetics, enabling the successive discovery of oncogenes and tumor suppressor genes, and contributing greatly not only to cancer research but also the life sciences as whole. At the same time, we joined forces with the government, taking part in its comprehensive strategy against cancer and advancing the crusade against the grim disease.

Of these efforts, the government strategy on cancer research probably worked most effectively and successfully in research on adult T-cell leukemia and HTLV. The discovery of the disease and its pathogen virus, and the implementing of preventive measures and development of treatments were all accomplished by Japanese researchers. This is indeed a significant achievement made possible by the Kakenhi-funded strategy to combat cancer.

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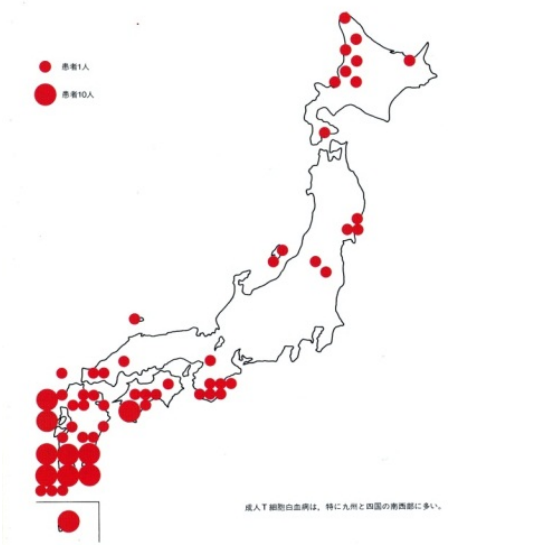

Figure 1 Distribution of Adult T-cell Leukemia Cases in Japan (1980s)

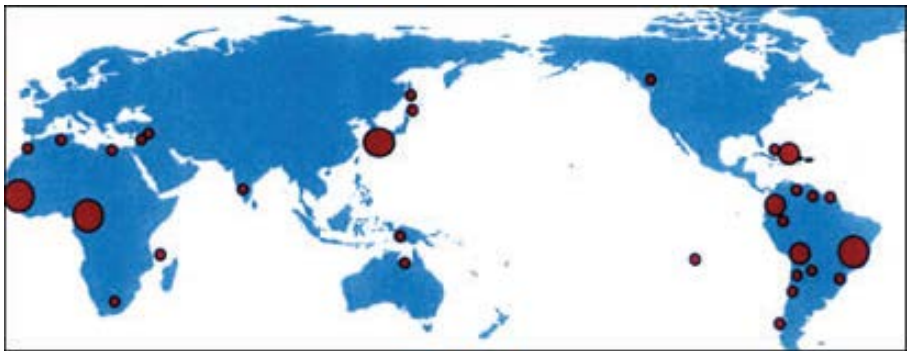

Figure 2 (World Map) Distribution of HTLV Carriers in the World

Figure 3 (Mummy) Mummy of the Andes Highlands (1500 years ago)

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Profile: Kuroki participated in the 10-year Strategy for Cancer Control programs from 1983 to 2003, as well as the Cancer Special Research and Cancer Research in Priority Areas projects. He became president of the Japanese Cancer Association in 2000.□