Abstract. The autoimmune disease interstitial pneumonia/dermatomyositis complex (ID) is classified as a paramalignancy since it is associated with a variety of malignancies at a high incidence in aged patients. We found a striking resemblance of pathophysiological features between ID and immunoendocrinopathy syndromes (IES) with depressed adrenocortical function. Drip infusion of megadose vitamin C, dehydroepiandrosterone and cortisol (an adrenocortical secretion substitute) was found to be effective for the control of ID. It has also been indicated that ID is a disease of adrenocortical insufficiency. Evidence is presented to indicate that ID in its clinical course is linked to environmental stress. The nature of paramalignant ID is discussed in the light of cancer epidemiology.

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The recent issue of Harrison’s text book of internal medicine presents an article on interstitial lung diseases (ILDs) by T. E. King who states: “These disorders are often associated with considerable morbidity and mortality, and there is little consensus regarding the best management of most of them” (1). King also adds that “ILDs have been difficult to classify because >200 known individual diseases are characterized by diffuse parenchymal lung involvement, either as the primary condition or as a significant part of a multiorgan process, as may occur in the connective tissue diseases (CTDs)” (1). As unknown causes, he nominates two examples together with a number of other diseases – polymyositis-dermatomyositis (PD) and chronic active hepatitis. Under the title of “Polymyositis, dermatomyositis and inclusion body myositis” in the same book, Delakas refers an associated disease of PD to “interstitial lung diseases which may precede myopathy or occur early in the disease and develop in up to 10% of patients with PD” (2). More importantly, aged patients with dermatomyositis (D) may develop malignancy at high incidence in the lung, ovary, breast, gastrointestinal tract and myeloproliferative system (2, 3). To the best of our knowledge, the emergence of malignancy in autoimmune disease is restricted to the interstitial pneumonia/dermatomyositis complex.

The purpose of the present review is to elucidate the nature of the above paramalignant disease complex using relevant information from endocrinology and cancer epidemiology.

Common Feature between ILD/D Complex and the Immunoendocrinopathy Syndromes (ICS)

The concept of immunoendocrinopathy syndromes (ICS) is derived from the two clinical cases of adrenal insufficiency in which a destructive lymphocytic infiltration of both thyroid and adrenal cortex was observed at autopsy (4). The above disease entity represents a number of autoimmune diseases including adrenocortical insufficiency, chronic active hepatitis, insulin-dependent diabetes mellitus, vitiligo and Parkinson disease. It may not be a mere coincidence that chronic active hepatitis is cited as a background disease in both ILD/D complex and the ICS (1, 4). In addition, the introduction of drip infusion including megadose vitamin C, dehydroepiandrosterone and cortisol (a fortified adrenocortical secretion substitute) was found useful for the control of ILD/D complex (5) – a finding indicating that ILD/D complex should be regarded as another adrenocortical insufficiency. Thus, both ILD/D and ICS turn out to be two autoimmune diseases sharing in common one hormonal disorder – insufficiency of adrenocortical function. Details of disease progression...
mechanism in ILD/D and ICS still remain to be further explored. Above all, the reason why the former is of paramalignant nature whereas the latter is not warrants further investigation.

Cancer Epidemiology and the Paramalignant ILD/D Complex

In 2004, we presented a review in which a set of age-adjusted cancer incidence rate (AAIR) per 100,000 data of the world was shown as follows: i) 350.0 for all sites, 119.1 for lung, 11.4 for colon, 25.3 for stomach in New Zealand Maori males. ii) 283.4 for all sites, 51.7 for lung, 30.9 for colon, 12.3 for stomach in New Zealand Caucasian males. iii) 329.6 for all sites, 96.1 for lung, 28.0 for colon, 24.3 for stomach in Hawaiian Hawaiian males. iv) 362.4 for all sites, 68.6 for lung, 31.7 for colon, 10.2 for stomach in Hawaiian Caucasian males. v) 317.5 for all sites, 62.2 for lung, 64.0 for breast, 13.7 for colon, 20.4 for stomach in New Zealand Maori females. vi) 248.0 for all sites, 15.7 for lung, 64.3 for breast, 30.5 for colon, 5.2 for stomach in New Zealand Caucasian females. vii) 278.9 for all sites, 39.5 for lung, 100.2 for breast, 13.7 for colon, 11.8 for stomach in Hawaiian Hawaiian females. viii) 309.6 for all sites, 36.1 for lung, 99.3 for breast, 23.6 for colon, 3.9 for stomach in Hawaiian Caucasian females (6). The decreasing ranking orders of AAIR for all sites are as follows: Hawaiian Caucasian male, New Zealand Maori male, Hawai Hawaiian male, New Zealand Caucasian male in the male population. Those in female population are as follows: New Zealand Maori, Hawai Hawaiian, Hawai Caucasian and New Zealand Caucasian. By cancer site, lung cancer ranks first in all four male populations, and breast cancer ranks first in all female populations. Information is also available to indicate that African-American males are more vulnerable to lung cancer and all site cancer than the corresponding Caucasian American in San Francisco (unpublished data). It has been suggested that social factors could be implicated in the emergence of the racial and geographical differences of cancer risk (6).

E. Farber (7) stated that “a positive association between the incidence of hepatocellular carcinoma and the consumption of alcoholic beverages has been reported in some countries. The possible mechanism of this association remains unclear, however”. There is no convincing evidence that alcohol can initiate the long multistage process of development of hepatocellular carcinoma. Thus, it may appear that alcohol cannot be considered as a carcinogen. The effects of alcohol were also compared with known promoting agents for liver cancer. Although the available data are not clear, nevertheless it appears that alcohol cannot be considered as a *bona fide* promoting agent for liver cancer development (7). His statement, as an experimental pathologist, corresponds well with a report from Mainland China concerning the risk factor for primary liver cancer (8). Luo et al. described ten risk factors related to primary liver carcinoma (PLC) in a Chinese population: cirrhosis, HBV infection, HCV infection, family history of liver cancer, unstable emotion, depressed characters, aflatoxin, alcoholic, intake of musty food and drinking contaminated pond water. They concluded that the main risk factors for PLC in China are liver diseases, family history of liver carcinoma, poor psychic status, aflatoxin, and some unhealthy behaviors (8).

In 2006, Baker et al. (9) investigated the relation between active/passive smoking and risk of ovarian cancer in Buffalo, New York. Their results indicated a decreased risk of ovarian cancer for nonsmokers exposed to ETS (environmental tobacco smoke), former smokers or current smokers (9). In 2008, Hosono et al. (10) reported a reduced risk of endometrial cancer from alcohol drinking in Japan. Thus, both nicotine and alcohol, two psychoactive compounds, reduce the risks of two types of female cancer. It might not be a mere coincidence that endometrial cancer and ovarian cancer represent two human neoplasias which have been associated with environmental stress, as deduced from their steroidal and epidemiological characteristics (11, 12).

Seldom has the relation between environmental stress and cancer risk been investigated. The present review investigates the nature of a paramalignant disease ILD/D complex as well as of its associated malignancies in the framework of the concept of the adaptation syndrome of Hans Selye.

Endocrinological Aspect of Disease Progression in ILD/D and Associated Malignancies

The model of the general adaptation syndrome presents three stages of stress progression: i) alarm reaction, ii) resistance, iii) exhaustion (13). There are three discriminating factors to be considered. In the stage of alarm reaction, the power of host resistance (R), the weight of the thymus (Tw) and the fat content of the adrenals (Af) drop as edema progresses (Ep). In the stage of resistance, R, Tw and Af each remain at their zenith levels but Ep remains at its nadir level (13). After entry into the stage of exhaustion, R, Tw and Af each follow a gradual decline and Ep rises (13). The adrenal cortex and the thymus are believed to play cardinal roles in the transition of the three stages. The clinical management of ILD/D mostly starts at the stage of resistance. It may be argued that the drip infusion system including megadose vitamin C, dehydroepiandrosterone (adrenal androgen) and cortisol, an adrenocortical secretion substitute, is useful for the control of ILD/D by protecting the functions of both the adrenal cortex and the thymus against the homeostatic mechanism. Clinically, it was found to be effective for the control of ILD/D (5) in spite of the long-term use of two steroids.
Another problem of ILD/D is the existence of persistent bacterial infection (pneumonia) in the morbid lung which may lead to devastation in spite of the drip infusion system. In some cases, the disease (pneumonia) remained well-controlled with intermittent use of antibiotics (unpublished data). The effectiveness of the drip infusion system also varied from one patient to another depending on the severity of lung lesion (unpublished data).

Entry into the stage of exhaustion occurred in some patients who failed to continue the use of the drip infusion system. The last stage took the form of either respiratory insufficiency or emergence of malignancy (3,14). The fact that appearance of malignancy in ILD/D complex is restricted to aged patients is related to the observation of immunologists who found that the size of CD8+ lymphocytes (suppressor T-cells), as assessed by FACS, was reduced in parallel with the progression of host age (15). It should be mentioned that estrogens may be responsible for the more active immune responses in females relative to males, and that the male hormone, dehydroepiandrosterone, prolongs life in females with a human autoimmune disease SLE (systemic lupus erythematosus) (16).

One may ask whether there is sufficient reason to indicate that ILD/D complex can be classified as a stress-linked disease of Hans Selye. We previously reported that the epidemic of ILD/D complex can be classified as a stress-linked disease (16). The above chronological coincidence between the emergence of a new disease epidemic and the economical recession in Japan is really remarkable.

Personal Experience

Mitsuod Kodama, has himself been afflicted with ILD/D since late summer of 1995. He now suffers from insulin-dependent diabetes mellitus, chronic active hepatitis and slight inclination to Parkinson disease in spite of the constant practice of his specific vitamin C + dehydroepiandrosterone + cortisol drip infusion system. It should be added that no malignancy has been reported among ILD/D patients under the protection of the specified vitamin C drip infusion system. Toshiko Kodama, the life-long partner of Mitsuod Kodama, was also afflicted with ILD/D in October 1995. She started megadose vitamin C drip infusion without either antibiotic therapy or dual steroidal annex (dehydroepiandrosterone and cortisol). In 2000, a breast cancer emerged at her right nipple.

After radical operation, she started the combined use of antibiotics and steroid-annexed vitamin C therapy. In 2002, a local tumor recurrence was noted. In late August of 2005, she passed away at the age of 75 with right pulmonary tumor metastasis (5). Retrospectively, the combined practice of consistent antibiotic therapy and the specified combination of megadose vitamin C, dehydroepiandrosterone and cortisol was found worthy of serious consideration.

References


Kodama and Kodama: Paramalignancy and Stress (Short Review)