CLINICO-PATHOLOGICAL CONFERENCE

A case of generalized Hailey-Hailey disease with fatal liver injury

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Abstract. We report a case of a 59-year-old man with a severe generalized form of Hailey-Hailey disease that was complicated by fatal liver injury. Erosive lesions were first noted in the axillary and perianal regions at 15 year of age, and Hailey-Hailey disease was diagnosed based on the clinical features and histologic findings in skin biopsy specimens. The patient was treated with at first topical steroids and later a low dose of a corticosteroid, but the skin lesions gradually became generalized. At 45 years of age liver dysfunction was detected after azathioprine and vinblastine treatment for the generalized skin lesions. The liver injury gradually progressed and finally the patient died. The gene responsible for Hailey-Hailey disease was recently identified as *ATP2C1*, and it encodes a Ca^{2+}-transport ATPase with broad expression, including in skin and liver. This finding suggests that mutation of the *ATP2C1* gene may give rise to an extracutaneous phenotype, such as the liver dysfunction observed in severe cases, including our own. Further accumulation of cases is necessary to determine whether this is true. (Keio J Med 50 (2): 109–116, June 2001)

Dr. Amagai (Moderator): I now announce the opening of the 1009th clinico-pathological conference.

The case of Hailey-Hailey disease being presented today had problems both in the fields of dermatology and internal medicine. The patient had a long history of Hailey-Hailey disease, and I would like to first ask the dermatologist-in-charge to describe the course of this patient. Eventually, the patient died of liver injury, and I would like to ask Dr. Wakabayashi, the internist who treated the patient, to describe the course of the liver injury in the patient. Later, Dr. Hakuno will speak on the latest knowledge on Hailey-Hailey disease. Finally, Dr. Hashiguchi, a pathologist, will summarize the lesions associated with liver injury in the patient. I hope that by the end of our discussion, we can reach some reasonable conclusion as to the direction with which investigation of such cases must proceed.

Now, Dr. Masakazu Kobayashi will summarize the dermatologic course of the disease in the patient.

Dr. Kobayashi (Dermatology): The patient had a 45-year history of illness. I shall briefly describe the history of treatment of the case at the Department of Dermatology.

The patient was a 59-year-old man, who first noticed skin rashes in the axillary and perianal regions when he was 15 years old. At the age of 30, he was diagnosed as having Hailey-Hailey disease at another hospital. Despite intensive treatments including systemic steroid therapy, the patient was not completely cured of the disease, and at the age of 40, he visited our Department. At the first examination, fist-sized, well-demarcated whitish erosions with erythematous bases were observed bilaterally over the skin of the axillary and inguinal regions. Vesicles and pustules were also noted on or around the erythematous lesions (Fig. 1). Well-demarcated erythematous lesions of various sizes, up to the size of a human fist, were also distributed diffusely over the trunk.

The patient was treated with oral etretinate (50 mg/day) and topical steroid therapy. However, since no improvement was noted, etretinate administration was discontinued. Oral prednisolone therapy (30 mg/day) was started, and the skin lesions showed some improvement. However, the skin lesions recrudesced

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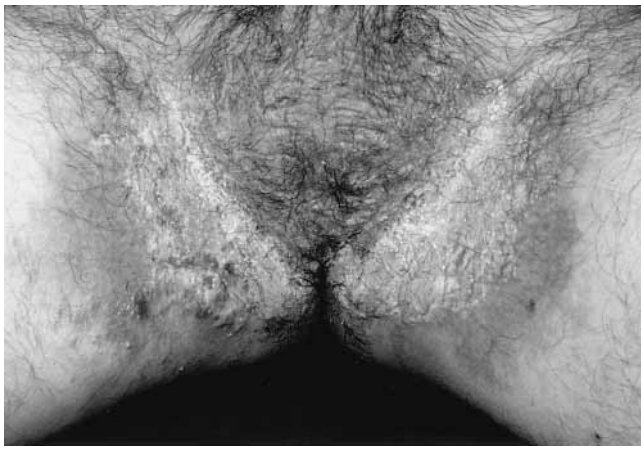


Fig. 1 Erythema with maceration are recognized on the groin, include small linear erosions and flaccid blisters.

when the dose of prednisolone was reduced to 15 mg/day, and oral azathioprine at 100 mg/day was added to the treatment regimen; oral doxycycline hydrochloride was also added because of secondary bacterial infection of the skin lesions. Thereafter, however, the patient developed hepatic dysfunction, and under the suspicion of drug-induced hepatitis, azathioprine and doxycycline hydrochloride administration was discontinued, and the hepatic function returned to normal.

When the patient was 45 years old, he developed a fever of 39 °C, and fungi and bacteria were cultured from the skin lesions. Therapy with flucytosine and amikacin was started, however, the patient again developed hepatic dysfunction. Under the suspicion of drug-induced hepatitis, the dose of prednisolone was increased to 30 mg/day. The hepatic function returned to normal, and the dose of prednisolone was thereafter gradually decreased to 5 mg/day.

At the age of 46 when etretinate therapy was resumed, the patient again developed hepatic dysfunction. Subsequently, the patient developed repeated remissions and aggravations of the skin lesions. At the age of 49, prednisolone administration was discontinued, and the patient was put on topical steroid therapy and topical antibiotic ointment application. When the patient was about 54 years old, slightly elevated, well-demarcated, indurated multiple erythematous lesions with scales, measuring up to the size of a child's head, began to appear on the lower legs and the trunk (Fig. 2). At the age of 55, the skin lesions worsened abruptly, and erythema with yellow-white scales spread over almost the entire body, associated with the development of fever. Foul-smelling exudative and erosive lesions developed on the lumbar and femoral regions. Since the fever was thought to be due to infection or skin inflammation, combined treatment with prednisolone of 30 mg/day and antibiotics was started, and successful resolution of the fever and marked improvement of the skin lesions were noted. The skin lesions began to worsen again when the patient was about 58 years old, with the lesions extending over large areas of the trunk and extremities, and development of erythroderma on the lower half of the body (Fig. 3). When the patient was 59 years old, he developed hepatic dysfunction once again, associated with weight loss, and was admitted to the Department of Internal Medicine of our hospital.

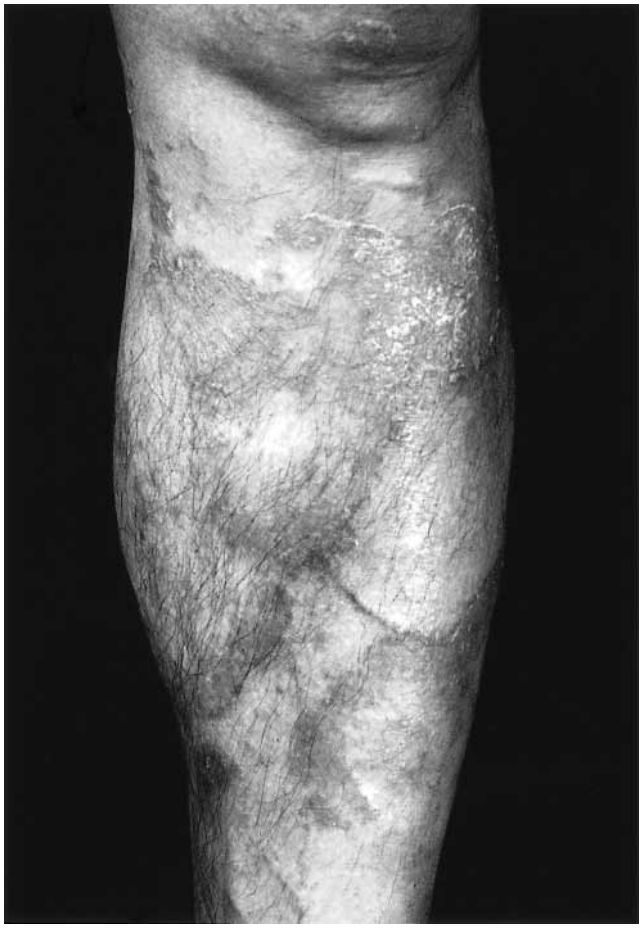


Fig. 2 Erythematous, sharply marginated and scaly plaques are recognized on the legs. They produce annular lobulated figures.

Dr. Amagai: Thank you very much for your description of the case, Dr. Kobayashi.

The patient initially had characteristic skin lesions on the axillary regions and the groins, typical sites of lesions in Hailey-Hailey disease, and over time, the lesions extended over the entire body, as described by Dr. Kobayashi. What disease would you suspect from such a dermatologic presentation?

Mr. Honaga (6th year student): I would suspect tinea or candidiasis.

Dr. Amagai: In this patient, characteristic skin lesions were observed over the entire body, with the

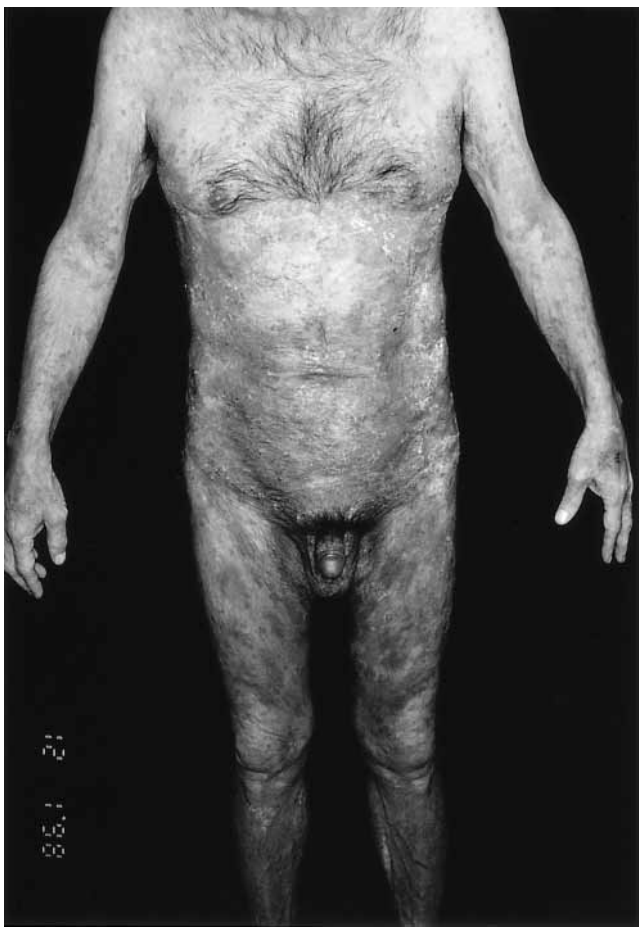


Fig. 3 Generalized erythemas are recognized on the trunk and extremities, and profuse scales are seen particularly on the trunk.

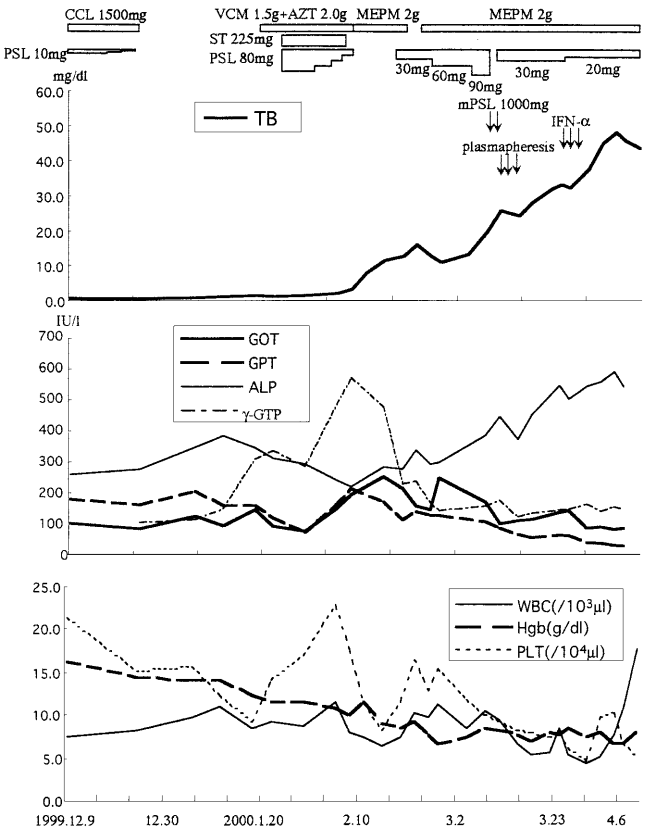


Fig. 4 Clinical course of the patient. CCL: Cefaclor, PSL: Prednisolone, VCM: Vancomycin, mPSL: Methyl Prednisolone, AZT: Aztreonam, ST: Sulfamethoxazole-trimethoprim, MEPM: Meropenem.

eventual development of erythroderma, in which a majority of the skin surface becomes reddish and peels off. Erythroderma occurs by numerous causes, including atopic dermatitis, autosensitization dermatitis, and psoriasis. We, in fact, considered psoriasis as the most probable diagnosis in this case at the beginning. There are also other diseases that are associated with erythroderma, e.g., pityriasis rubra pilaris, pemphigus foliaceus, infections, malignant lymphoma, and Sezary syndrome. Erythroderma can also be induced by drugs. Thus, there are numerous causes that one must think of when one sees a patient with erythroderma.

In summary, the patient initially presented skin lesions typical of Hailey-Hailey disease. Because of the development of psoriasis-like lesions over the entire body, immunosuppressive agents and etretirate were used in this patient. In the course of such drug treatment, hepatic dysfunction developed and eventually became the main feature in this patient.

Next, Dr. Wakabayashi, the internist-in-charge of the patient, will briefly describe the course of illness in the patient from the first onset of hepatopathy until his death.

Dr. Wakabayashi (Internal Medicine): I shall describe the medical course of the patient (Fig. 4). This patient suffered repeatedly from drug-induced hepatitis, and was referred to the Department of Gastroenterology of our hospital. In July 1993, he was found to be positive for serum HCV antibody. He was thus diagnosed as having chronic type-C hepatitis, and required repeated hospital admissions. In December 1998, when he was an inpatient at the dermatology ward, common cold-like symptoms developed on December 31, and slight fever on January 3, 1999, with increasing serum levels of markers of inflammation. On January 12, the patient developed fever of 38°C Celsius and cough, and chest radiography showed a ground-glass opacity in the right upper lung field. CT revealed a ground-glass opacity and cavitary nodular shadows. Intravenous infusion of vancomycin and aztreonam (Azactam) was initiated on January 21, however, the patient's respiratory function worsened, with a decrease of pO_2 to 56 Torr. The results of lung perfusion scintigraphy ruled out the diagnosis of pulmonary embolism.

Bronchoscopy was performed. *Pneumocystis carinii* was found in bronchoalveolar lavage specimens, and

intravenous infusion of pentamidine 4 mg/kg/day was initiated for the treatment of *Pneumocystis carinii* pneumonia. Administration of prednisolone at 80 mg/day was begun on January 28 when the respiratory function worsened. Thereafter, with improvement of the respiratory function, the dose of prednisolone was reduced to 20 mg. Bradycardia, presumably an adverse effect of pentamidine, was noted on February 3, and pentamidine was replaced by ST mixture. Hepatic dysfunction was noted on February 6, with increased serum levels of GOT and GPT. Under the suspicion of drug-induced hepatopathy, vancomycin and aztreonam were discontinued. The dose of pentamidine was also reduced, and the drug was discontinued on February 7. Despite these measures, however, the serum total bilirubin level increased to 5.8 mg/dl. Because the patient had a history of cholelithiasis, abdominal ultrasonography was performed. Since the diagnosis of cholelithiasis and cholecystitis was confirmed, meropenem (Meropen) therapy was started. However, despite this therapy, the serum total bilirubin level remained high, with a predominance of direct bilirubin, and endoscopic retrograde cholangiopancreatography (ERCP) was performed keeping in mind the possibility of obstructive jaundice, and the ENBD tube was retained.

Despite all these measures, jaundice persisted, and the serum bilirubin level continued to rise. Therefore, prednisolone at the dose of 30 mg/day was begun on February 17. Although there was temporary improvement, however, the serum bilirubin level began to increase again. The dose of prednisolone was, therefore, increased to 60 mg/day on February 24. Since the patient remained unresponsive to the treatment, glucagon insulin therapy was started on March 4, and the dose of prednisolone increased to 90 mg/day on March 6, both of which eventually proved to be ineffective. Steroid pulse therapy with methylprednisolone of 1 g/day was started on March 9, with no improvement, and with the continued increase of the serum bilirubin level, plasmapheresis was begun on March 11, and performed 5 times. The bilirubin level improved immediately after plasmapheresis, but increased to the pretreatment level on the following day, showing that plasmapheresis was only temporarily effective. We suspected the possibility of acute aggravation of chronic type-C hepatitis, besides drug-induced hepatopathy. Based on this presumption, intramuscular injection of IFNα (9MU/day) was begun on March 25. The serum transaminase levels improved temporarily, but because of the development of adverse reactions (fever exceeding 39 degrees Celsius, general malaise and tachycardia), INF dose was reduced to 6MU daily. However, the adverse reactions persisted, and IFN therapy was discontinued after three sessions under judgment that the patient would not be able to tolerate the full course of the treatment. The bilirubin level continued to increase, with the total bilirubin level reaching 48.2 mg/dl on April 4. Then, acute renal failure, presumably reflective of multiple organ failure, developed, and the patient died on April 11. We first considered drug-induced hepatopathy as the cause of death, however, I believe that some other diseases must also be considered. The patient was known to have chronic type-C hepatitis. Is there a possibility that the hepatopathy was caused by other viral cause than type-C hepatitis?

Mr. Funao (6th year student): Type-B hepatitis and EB virus-induced hepatitis could be other possible causes of the hepatopathy.

Dr. Wakabayashi: Type-B hepatitis, like type-C hepatitis, can be associated with acute changes. Considering the medical history of the patient, the possibility of type-A hepatitis is remote. EB virus and cytomegalovirus can be other possible causes of the hepatopathy. The patient had very low lymphocyte counts, in particular of the CD4 cells. Initially, we suspected HIV infection as the predisposing factor for *Pneumocystis carinii* pneumonia, but the patient was found to be negative for HIV antibody in the serum. At one point, the CD4 cell count was below 20/μl, and cytomegalovirus antigenemia was positive. Therefore, cytomegalovirus infection could be reasonably considered as a possibility.

In regard to drug-induced hepatopathy, the most strongly suspected causative drug was pentamidine. In addition, the antibiotics vancomycin and aztreonam cannot be ruled out as other possible causes. It is also possible that meropenem, administration of which was started after the onset of hepatopathy, further exacerbated the hepatopathy.

Next, concerning the aggravation of chronic type-C hepatitis, the reserve capacity of the patient's liver at the time of admission was not very poor in terms of the results of the ICG test (5.3%). Therefore, it is not likely that the patient had very advanced hepatopathy when he was first examined. However, the patient had developed various complications and received steroid therapy. It is possible that the type-C hepatitis became aggravated when steroids were used in large doses. It has been reported that a patient with chronic type-C hepatitis who was on high-dose steroid therapy died of fulminant hepatitis due to abrupt aggravation of the hepatitis following rapid tapering of the steroid dose.[1] However, the steroid therapy for *Pneumocystis carinii* pneumonia in this patient was aimed to improve the respiratory function rather than to eliminate *Pneumocystis carinii*. Therefore, reasonable tapering of the steroid dose was executed. Moreover, since the patient had diabetes, the attending doctor in the Department of Respiratory Medicine attempted tapering of the steroid dose as early as possible.

Dr. Amagai: Now, I would like to summarize the features of the case in order to reach the conclusion. In this patient, numerous drugs were used, and more and more drugs were added, the hepatitis became worse. There were several possible causative drugs. Viral causes were also possible. The patient in fact had type-C hepatitis. Thus, there are various possibilities. Drug-induced hepatitis was first suspected, and type-C hepatitis was considered later. I would like to invite opinion regarding the relationship between these two conditions. In addition, is there any possibility that the hepatopathy in this patient was derived from any cause other than drug and virus?

Dr. Wakabayashi: We can definitely not exclude the possibility of drug-induced hepatopathy. Since drug-induced hepatopathy is only diagnosed after excluding other causes, its possibility can never be disregarded. As mentioned previously, high-dose steroid therapy was used for the treatment of chronic type-C hepatitis. Considered together with the poor immunocompetence of this patient, it is quite possible that acute aggravation of chronic type-C hepatitis was the actual cause of the hepatopathy in this patient.

Dr. Amagai: Is it possible that the use of multiple drugs caused the hepatopathy?

Dr. Wakabayashi: Sure it is. Since this patient developed hepatopathy following the administration of various drugs, it is indeed possible that multiple drug use was responsible for the hepatic dysfunction.

Dr. Amagai: Let us go back to the issue of Hailey-Hailey disease. Hailey-Hailey disease is a hereditary disease. Since it is inherited as an autosomal dominant disease, it is possible that a single gene is responsible. Despite the intensive effort made at genetic analysis of this disease during the past decade, the gene responsible for Hailey-Hailey disease was identified just a few months ago.[2] Dr. Hakuno will speak on the latest knowledge on Hailey-Hailey disease.

Dr. Hakuno (Dermatology): Hailey-Hailey disease, or familial benign chronic pemphigus, falls into the category of inherited skin disorders of keratinization, and is inherited as an autosomal dominant disease. Although there are no skin symptoms at birth, the patients develop skin symptoms after adolescence, usually when they are in 20s–30s.

As to the clinical picture, itchy erythema occurs in friction areas, i.e., nuchal, axillary, inguinal, and perianal regions, and lesions may fuse to form plaques, and may be associated with blisters, erosions, scales, or pigmentation. Lesions may often be moist and exudative, with a foul-smelling exudate. This disease follows a chronic course of repeated remissions and exacerbations. The skin lesions often become aggravated in the summer season and extend over the entire body surface, because of the high temperature and humidity, ultraviolet light exposure, or secondary infection.

Clinical differential diagnoses include seborrheic dermatitis, cutaneous candidiasis, and tinea corporis. If fungal tests are negative, and the family history, age at onset, and clinical course are suggestive, the diagnosis should be established by skin biopsy.

Histopathologically, this disease is characterized by acantholysis, often in the pattern of a dilapidated brick wall. Acantholysis is considered to be derived from incomplete intercellular adhesion resulting from the degeneration or disappearance of proteins which constitute the cell-cell adhesion mechanisms, such as desmosomes or adherens junctions, present among the cells in the epidermal prickle cell layer.

Diseases with acantholysis as a major feature are broadly divided into autoimmune diseases and hereditary diseases. Pemphigus represents the major disease of the former group. Currently, pemphigus vulgaris and pemphigus foliaceus are diagnosed by demonstration of the presence of antibodies in the serum against desmoglein 3 and desmoglein 1, respectively. On the other hand, the prototypes of the hereditary disease group are Hailey-Hailey disease and Darier's disease. Although it is known that the Hailey-Hailey disease gene is present at 3q21–q24, and the Darier's disease gene at 12q23–q24.1, the genes themselves had not been identified for a long time. However, it has recently become apparent that Hailey-Hailey disease and Darier's disease are caused by mutation of the ATP2C1 and ATP2A2 genes, respectively, both of which are genes encoding the ATP-dependent Ca^{2+} pump, which regulates the intracellular Ca^{2+} concentration.[2,3] There are a number of Ca^{2+} pumps in the cytosol that regulate the intracellular Ca^{2+} concentration. The Ca^{2+} pump present in the Golgi apparatus is encoded by ATP2C1, and the Ca^{2+} pump present in the endoplasmic reticulum is regulated by ATP2A2. It is not yet clear as to which type of mutations of ATP2C1 and ATP2A2 in Hailey-Hailey disease and Darier's disease result in acantholysis. However, it is presumed that dysfunction of the Ca^{2+} pump leads to high intracellular concentrations of Ca^{2+}. It is known that intracellular Ca^{2+} in epidermal cells plays a very important role in the differentiation of the epidermis and intercellular adhesion. It is possible that impaired regulation of the intracellular Ca^{2+} concentration causes abnormal differentiation of epidermal cells, activation of various enzymes, and degeneration or disappearance of Ca^{2+}-dependent proteins present in the desmosomes and adherens junctions (e.g., desmoglein, desmocollin, E-cadherin and P-cadherin), resulting in acantholysis. Interestingly, ATP2C1 expression has also been observed in various other organs besides the skin, including the liver, pancreas and kidney, and theoretically, patients with Hailey-Hailey disease may have involvement of other

organ systems as well, besides the skin. Although so far no involvement of other organ systems has been demonstrated in Hailey-Hailey disease, further careful collection and analysis of clinical cases are necessary.

Since Hailey-Hailey disease is a hereditary disease, treatment is conservative and symptomatic. The basic treatment is topical steroid therapy combined with topical antibiotic ointment application, aimed to control the skin lesions and to prevent secondary infection. When secondary infection is present, oral or intravenous antibiotic therapy may be indicated. In addition, topical application of activated vitamin D3 derivatives, oral therapy with vitamin A derivatives, and abrasion using CO_2 laser have also been reported to be effective.

Dr. Amagai: Thank you, Dr. Hakuno. It was a good and concise summary of the latest knowledge on the disease.

As Dr. Hakuno has just said, Hailey-Hailey disease is a hereditary disease. One of the characteristic features of the disease is that its onset is delayed after birth, manifesting when the patients are in their teens, 20s or 30s, similar to, for example, the case in Huntington's chorea, where the patients have no characteristic symptoms at birth, but develop neurological symptoms when they turn 30–40 years old. There are many other hereditary diseases of the skin. In the most well-known of them, epidermolysis bullosa simplex, blisters occur because cell-to-cell adhesion in the skin is impaired due to mutations in keratin genes. Patients with this disease already have blisters when they are born. In contrast, patients with Hailey-Hailey disease appear normal at birth. The cell-to-cell adhesion disorder becomes apparent in friction areas only when the patient is in his or her teens or the second or third decade. This is one of the very unique features of Hailey-Hailey disease.

There is another characteristic feature of Hailey-Hailey disease that deserves to mention. As Dr. Hakuno has pointed out, in cases of epidermolysis bullosa simplex caused by mutation of the keratin gene, the disease is manifested only in the skin. Other organ systems are not involved. In Hailey-Hailey disease, however, it has been found that the responsible gene is present not only in the skin but also in other organs. Nonetheless, there are no reports so far in the literature documenting abnormalities in other organs. This could also be because no attempts have been made so far to study the pathology in the other organs. Although the disease is a hereditary disease, the severity of the symptoms varies among individual patients according to differences in the types of mutations and individual genetic backgrounds. The patient discussed here today represents a considerably severe case of Hailey-Hailey disease. Therefore, it cannot be completely ruled out that the genetic abnormality itself was responsible for the skin manifestations as well as the hepatic dysfunction in this patient. It may be necessary to take this into consideration when encountering the disease in the future.

Finally, Dr. Hashiguchi, a pathologist, will speak about the lesions associated with the hepatopathy, with brief reference to the skin lesions. Dr. Hashiguchi, would you present the pathological aspect of this disease to the audience, please?

Dr. Hashiguchi (Pathology): The pathological diagnosis is shown in Table 1. There were multiple erosions and crusts on the skin over the entire body. Acantholysis and hyperkeratosis were observed histologically. A liver biopsy specimen obtained in January 1999 showed mild inflammation in the portal area and steatosis. However, macroscopic examination of the liver at autopsy revealed cholestasis and fibrosis (Fig. 5). Chronic cholecystitis and cholelithiasis of the gallbladder were also noted, but there was no acute suppurative inflammation or mechanical obstruction of the extrahepatic duct that would explain the cholestasis. Histologically, massive loss of hepatocytes and marked fibrosis were observed in the liver (Figs. 6, 7), and in some regions, regenerating hepatocytes exhibited nodular growth (Fig. 8). These histological changes led us a diagnosis of subacute hepatic injury, but its cause could not be determined from the histopathological findings.

Dr. Amagai: Are there any questions or comments that you would like to make on this case in general?

Mr. Honaga: The patient eventually died of renal failure; what was the cause of the renal failure?

Dr. Wakabayashi: The patient had severe hyperbilirubinemia, with the total bilirubin level in the serum eventually exceeding 40 mg/dl. Such severe and persistent hyperbilirubinemia is well known to induce multiple organ failure, in particular, renal failure. This could explain the occurrence of the acute renal failure in this patient.

Mr. Narumi (6th year student): Although Hailey-

Table 1 Pathological Diagnosis

1. Hailey-Hailey disease (29 years after the onset of symptoms)
2. Drug-induced hepatic injury + chronic hepatitis, type C
   1) Hepatic fibrosis and cholestasis, severe
   2) Jaundice
   3) Splenomegaly (250 g)
3. Aspergillosis
   Abscess formation in the following organs:
   lung, right (650 g), upper lobe; kidney, bilateral (170: 160 g); myocardium (510 g); left ventricle; urinary bladder; and thyroid gland (28 g)
4. Diabetus mellitus; Hyalinization of the pancreatic islets
5. Pulmonary congestion and edema, bilateral (490: 650 g)
6. Cardiac hypertrophy (510 g)
7. Aortic atherosclerosis, moderate
8. Chronic cholecytitis + Cholelithiasis; multiple stones (max. $1.4 \times 1 \times 1$ cm)

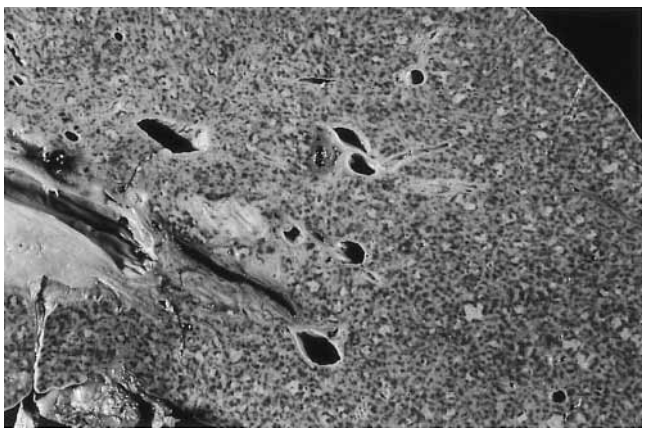


Fig. 5 Liver showed sever cholestasis and fibrosis.

Hailey disease is known to be an autosomal dominant disease, this patient had no family history. I would like to know how often patients with this disease do have a family history, if such data are available.

Dr. Amagai: This is a good question from the practical viewpoint. In general, sporadic cases can occur among all autosomal dominant diseases. In simple terms, in autosomal dominant diseases, when the sperm of the father or the ovum of the mother has the genetic mutation, the offspring manifests the disease. Viewed in a more complex manner, it is possible that cells with and without the mutated gene are mixed in a mosaic state, or there is genetic mosaicism.

Mr. Narumi: Were the children of this patient examined?

Dr. Nishikawa (Dermatology): The patient had three sons. One of them presented to our Department with eruption. However, on examination it was ordinary eczemas. None of the family members of the patient was diagnosed to have Hailey-Hailey disease.

Dr. Amagai: How old are the children now?

Dr. Nishikawa: They are all grown up. The boy I saw was 15 or 16 years old at the time of the examination.

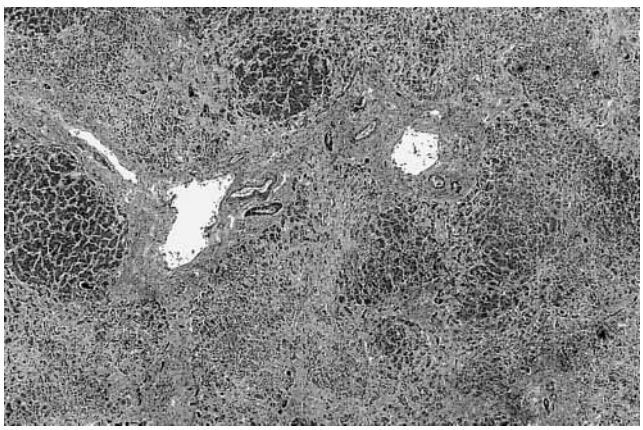
Dr. Amagai: Is it possible that the sons might develop the disease in the future?

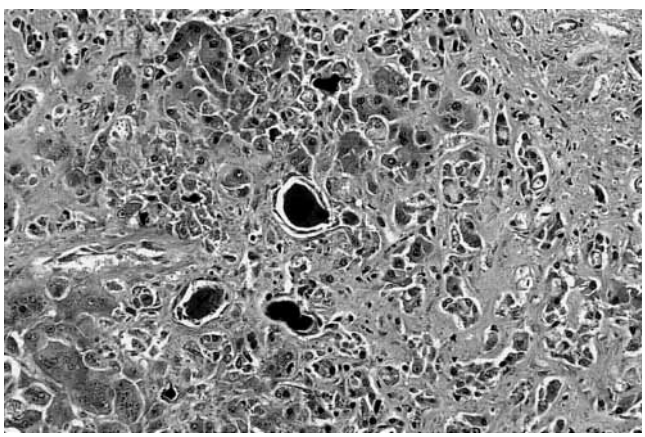
Dr. Nishikawa: I can only say that none of the patient's three sons have developed the disease to date.

Dr. Amagai: So the children of this patient have not manifested the disease until now. Are there any other questions or comments?

Mr. Tamura (6th year student): I understand that Hailey-Hailey disease characteristically manifests itself when the patient is in his 20s–30s. Considering that the skin lesions occur most frequently in the friction areas, could there be involvement of some other factors such as extrinsic stress?

Dr. Amagai: Although the gene responsible for the disease has been identified, and the disease is characterized by the eventual development of acantholysis, the events leading up to this process, or the underlying mechanism at the molecular level, remain completely unknown. As Dr. Hakuno mentioned, there is an interesting treatment strategy, namely, skin abrasion, which





Figs. 6, 7 Histologic examination of the liver. With acute injury, hepatocytes were ''dropped out'' and fibrosis were marked. Sever cholestasis was seen. (a: HE, ×40, b: HE, ×100)

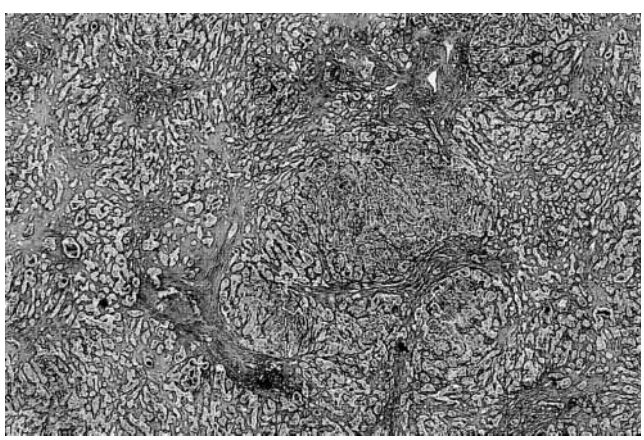


Fig. 8 Hepatocyte regenarative nodules were seen. (Silver stain, ×40)

has been employed for the treatment of mild and highly localized cases. In this treatment, the skin in the affected region is removed, and then allowed to regenerate. Although the disease may recur later, there is a temporary relief from the symptoms of the disease. This could be due to removal of some possible cumulative effect existent on stem cells. Therefore, it is speculated that the disease is manifested as a result of some cumulative abnormality in the stem cells.

Dr. Nishikawa: Dr. Hakuno, you mentioned that the ATP2C1 gene is expressed in the liver, but what is the level of expression of the gene in the skin and the liver?

Dr. Hakuno: The organs were cited in descending order of the level of expression, that is, skin, kidney, liver and so on. Thus, the level of expression in the liver is relatively high.[2]

Dr. Amagai: Now, I would like to conclude the conference. This patient presented here was a very severe case of Hailey-Hailey disease. It is reasonably certain that the patient had drug-induced hepatitis along with type-C hepatitis. However, is it also possible that the patient's liver injury was caused by the gene responsible for Hailey Hailey disease?

This patient with Hailey-Hailey disease had worsening hepatopathy over a long clinical course. In general, the disease, also referred to as familial ''benign'' chronic pemphigus, may run its course as a benign disease when the lesions are localized. However, there are some cases with severe disease. Besides the case reported here, Dr. Nishikawa has introduced the Okayama University's case of a patient who finally died of hepatopathy after a long clinical course during which the severity of the skin lesions paralleled that of the hepatic dysfunction. Taking these into consideration, although drug-induced hepatopathy is a strong possibility in this case, there still remains the question of whether the hepatic dysfunction was a result of mutation of the gene responsible for Hailey-Hailey disease gene. I would like to ask the pathologist for his comments on this.

Dr. Hashiguchi: In some autopsy cases, histological examination of the liver shows subacute hepatic injury, but the cause is unknown. In the present case, it would be difficult to attribute the hepatic damage to either drugs or type C hepatitis. Subacute hepatic injury has been often observed in type B acute hepatitis, however the patient was negative. There was no clear cause of the subacute hepatic injury in the present case, however, the genetic change seen in Hailey-Hailey disease may have contributed to the hepatic injury. So, this was an important case.

Dr. Amagai: Thank you. Various possibilities as to the cause of the hepatopathy in this case have been described. Are there any comments from the viewpoint of the internist on the possibilities presented?

Dr. Wakabayashi: It is possible that the gene responsible for Hailey-Hailey disease is expressed in the liver, and some triggering factor causes the hepatopathy to manifest. However, I cannot say anything definitively because of the lack of availability of substantial data.

One thing that I can say definitely is that while the liver function was not very poor at the time of admission even though the patient had chronic hepatitis, the hepatic cirrhosis was very severe at the time of autopsy. Considering that the biliary stasis and fibrosis were severe, it would not be unreasonable to consider that there were some other factors involved, although it is possible that the biliary stasis accelerated the development of hepatic cirrhosis.

Dr. Amagai: The patient presented here had Hailey-Hailey disease, a very rare hereditary disease. And among the cases of Hailey-Hailey disease, this case was of particular relevance, because he had severe disease and eventually died of hepatopathy.

In summary, as a dermatologist, I would like to point out that while any changes in the skin can be observed directly, for example, if the skin becomes red, we can see it, in the case of hepatic dysfunction, the liver changes may be overlooked unless laboratory abnormalities come to light. Thus, it is possible that changes similar to those present in the skin were also present in the liver or other organs, even though they were subclinical. However, examination of other organ systems, e.g., by liver biopsy would not be done, without definite indication. Concerning Hailey-Hailey disease, there has hardly been any case of hepatic dysfunction reported previously in the literature, except for the case of Okayama University. However, it is possible that subclinical changes do in fact occur in various organs, and that such changes are overlooked because we cannot see them directly. Thus, while concluding this 1009th C.P.C, I would like to emphasize that in this sense, the skin is a mirror reflecting the state of the internal organs.

Thank you for your kind attention.

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