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An autopsy case of fulminant Type 1 diabetes mellitus with lymphocytes infiltration of the thyroid gland and the pancreas

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ABSTRACT

We have been experiencing many autopsy cases of patients with high glucose- and acetone-concentration in the plasma. We performed an autopsy of a 47 year-old male without a medical history. He felt nausea and abdominal pain 5 days before his death, and had received medical treatment as the gastrointestinal disorder at a polyclinic hospital where his wife is working as a nurse. Two days after his admitting the hospital he felt the continuous nausea and visited another hospital. He was found dead in his bed in the next morning. There was no remarkable finding at autopsies except the edematous intestines. The biochemical analysis revealed high plasma glucose concentrations (over 666 mg/dl), relatively lower HbA1c level (5.2 %), slight elevation of serum pancreatic enzyme concentrations, high concentration of acetone, lower plasma C-peptide excretion, and no reactivity of anti GAD antibody. HE- and immuno-staining showed the severe lymphocytes infiltration in the pancreas and the thyroid gland. No reactivity with anti-insulin was observed in the pancreas. He probably died of fulminant type 1 diabetes reported mainly in Asia, especially in Japan, Korea and China. The significant feature of fulminant type1 diabetes is a remarkably acute onset and progression of hyperglycemia to severe ketoacidosis without apparent autoimmune pancreatic damage or long-term diabetes. Forensic pathologist should take notice of hyperglycemia in the performance of the autopsy in the sudden death cases and should make laboratory analysis and pathological examination including immuno-histochemical staining, since hyperglycemia might occur and decline the outcome of the non-diabetic patients with viral infection, hypothermia, acute stroke, subarachnoid hemorrhage, and/or septic or injury stress.

Keywords: Fulminant type 1 diabetes mellitus, Hyperglycemia, Sudden death

Introduction

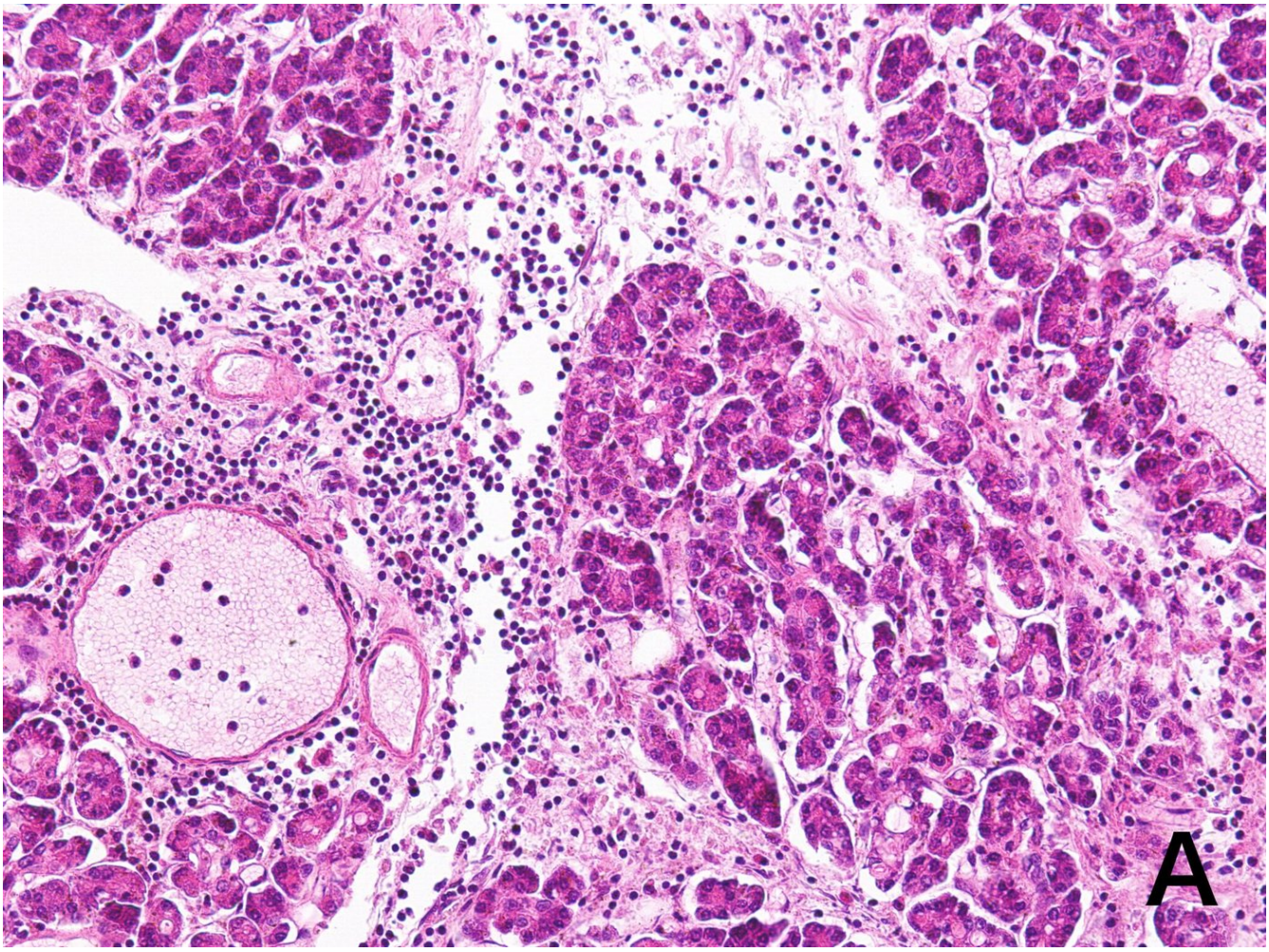
We have been experiencing many autopsy cases of patients with high glucose- and acetone-concentration in the plasma and urine. Diabetes mellitus (DM) is a chronic disease hallmarked by alterations in pancreatic insulin production or end-organ metabolism and divided in to Type 1 and Type 2 DM. Type 1 DM is an insulin-deficient status due to severe destruction of pancreatic beta cells, and is classified into two subtypes, type 1A and type 1B. Type 1A DM is caused by autoimmune mechanisms and is associated with islet auto-antibodies, such as the GAD antibody, whereas type 1B is not. In 1988, a study suggested that there might be a novel subtype of type 1 DM.[1] In 2000, this subtype, which had the same characteristics as the subtype discussed in the 1988 study, was described and named fulminant type 1 DM.[2] The clinical characteristics of fulminant type 1 are 1) remarkably abrupt onset of the disease, 2) very short (usually less than one week) duration of diabetic symptoms, e.g. polyuria and thirst, 3) the presence of acidosis at diagnosis, 4) negative findings for islet-related auto antibodies, such as islet-cell antibodies (ICA), anti-glutamic acid decarboxylase antibodies (GAD-Ab), and insulinoma-associated antigen 2 antibodies(IA-2-Ab), 5) virtually no C-peptide secretion (less than 10ug/day in urine), 6) elevated serum pancreatic enzyme levels, 7) frequently with flu-like symptoms around the time of disease onset, 8) association with pregnancy, and 9) strong association with HLA-DR4-DQ4 haplotype.[2] Although more than 250 patients with fulminant type 1 DM have been reported in Japan, few patients have been reported outside of Japan or Asia [3,4,5] and few autopsy reports have been made even in Japan. In this paper we report an autopsy cases of patient suspected fulminant type 1 DM.

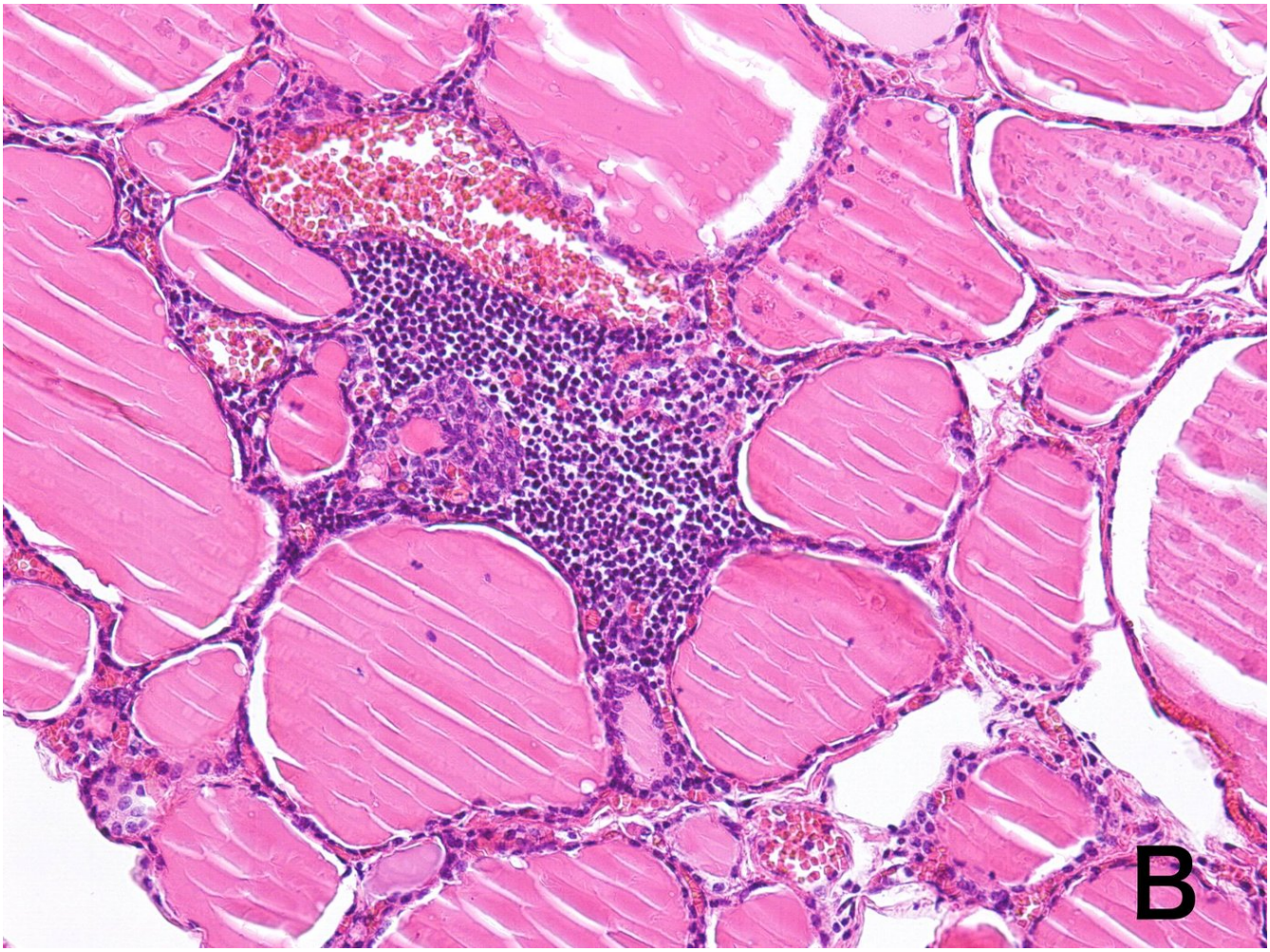
Case Report

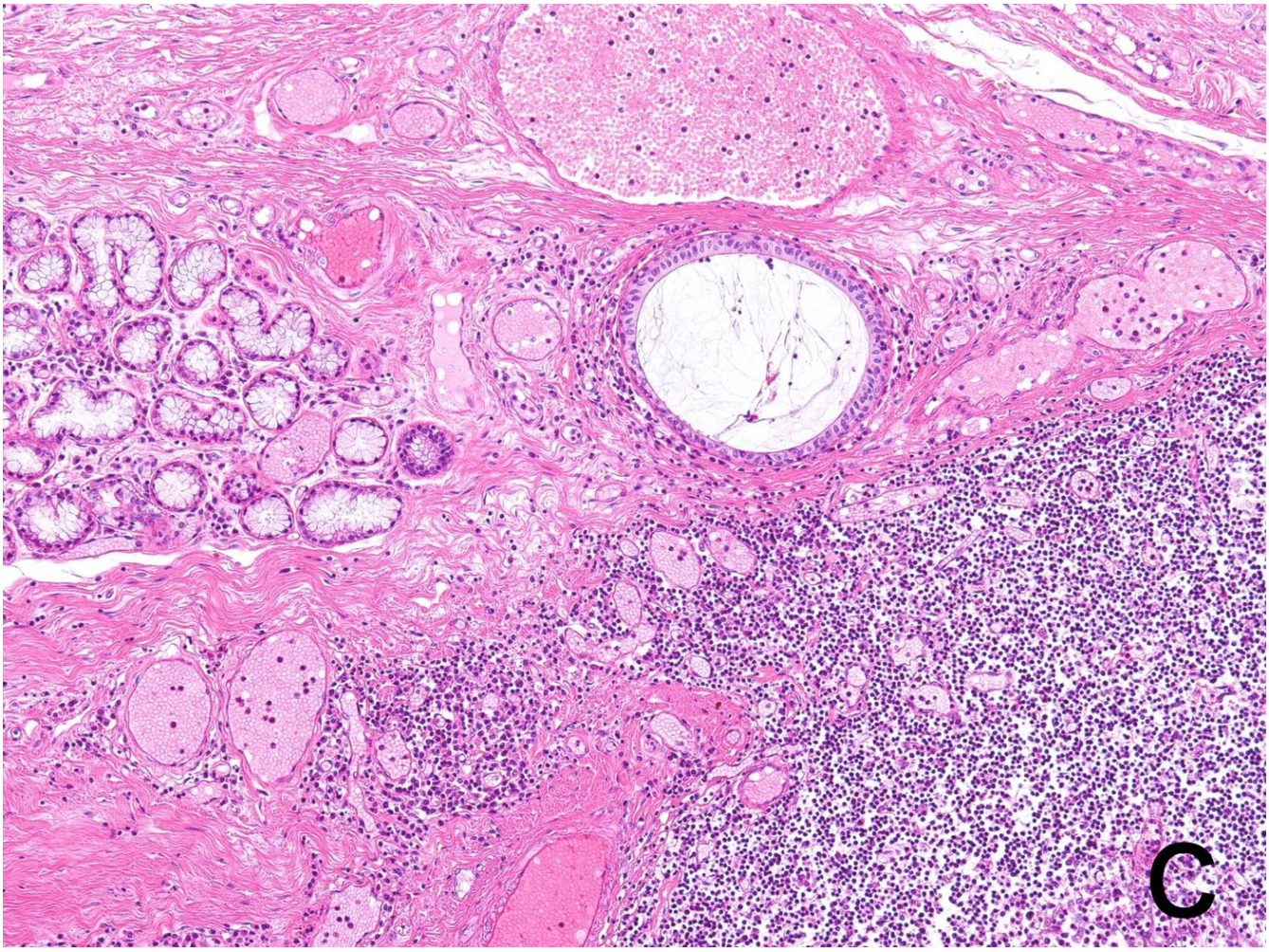
The cadaver was a 47-year-old Japanese man who has no past illness. He felt nausea and abdominal pain 5 days before his death, and had received medical treatment as the gastrointestinal disorder at a polyclinic hospital where his wife is working as a nurse. Two days after his admitting the hospital he felt the continuous nausea and visited another hospital. He was found dead in his bed in the next morning. In autopsy there was no remarkable finding excepting slightly edematous pancreas and intestines with small amount of ascites. The plasma glucose was excess 666mg/dl (over the detection limits), whereas HbA1c was 5.2% and plasma C-protein was 0.39ng/ml. Anti GAD-Ab was not detected in the plasma. Plasma amylase level increased to 834u/l. Other laboratory data were as follows: ALT1335u/l, ALP267u/l, TBIL0.6mg/dl, BUN45mg/dl, Chol167mg/dl, CRE3.1mg/dl, ALB3.0g/dl, GLOB4.6g/dl, Ca++9.8mg/dl, K+5.3mmol/l, Na+113mmol/dl. Although no alcohol was detected, high concentration of acetone was detected in the blood and the urine, 40.7ug/ml and 45.6ug/ml, respectively. Laboratory data were summarized in Table 1.

Table 1. Laboratory finding in present case at autopsy

Height (cm) / weight(kg)	170 / 49.4
BMI	17.1
Plasma glucose concentration (mg/dl)	666 (over detection limit)
Hba1c (%)	5.2
AMY(U/l)	834
Plasma C-protein (ng/ml)	0.39
Anti GAD-Ab	(-)
Acetone (ug/ml)	40.7
Acetone from urine (ug/ml)	45.6
ALP (U/l)	267
ALT (U/l)	1335
TBIL(mg/dl)	0.6
BUN (mg/dl)	45
Cholesterol (mg/dl)	167
CRE (mg/dl)	3.1
Albumin (g/dl)	3.0
Globuline (g/dl)	4.6
Ca ion (m mol/l)	9.8
K ion (m mol/l)	5.3
Na ion (m mol/l)	113


A


B


C

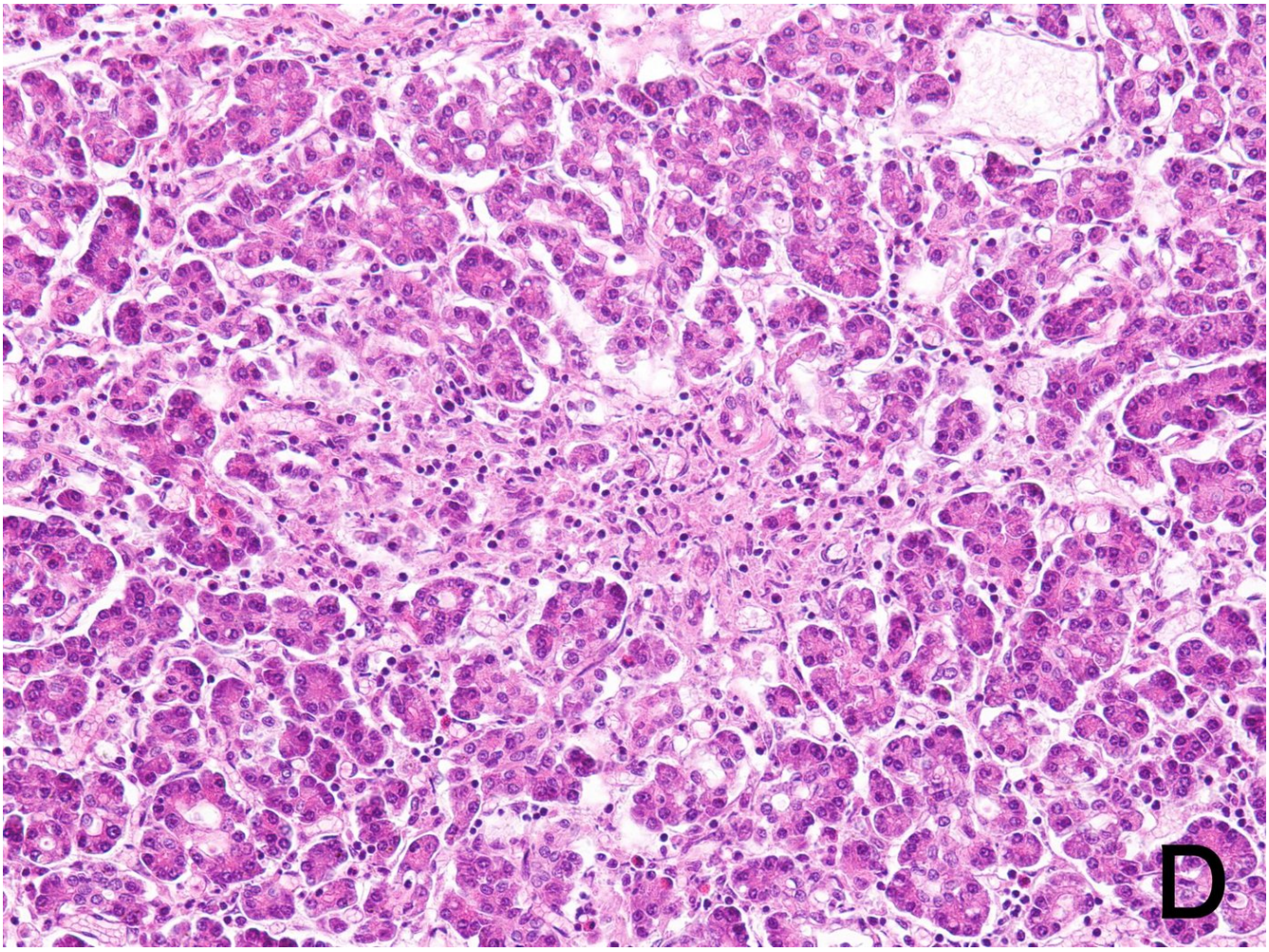
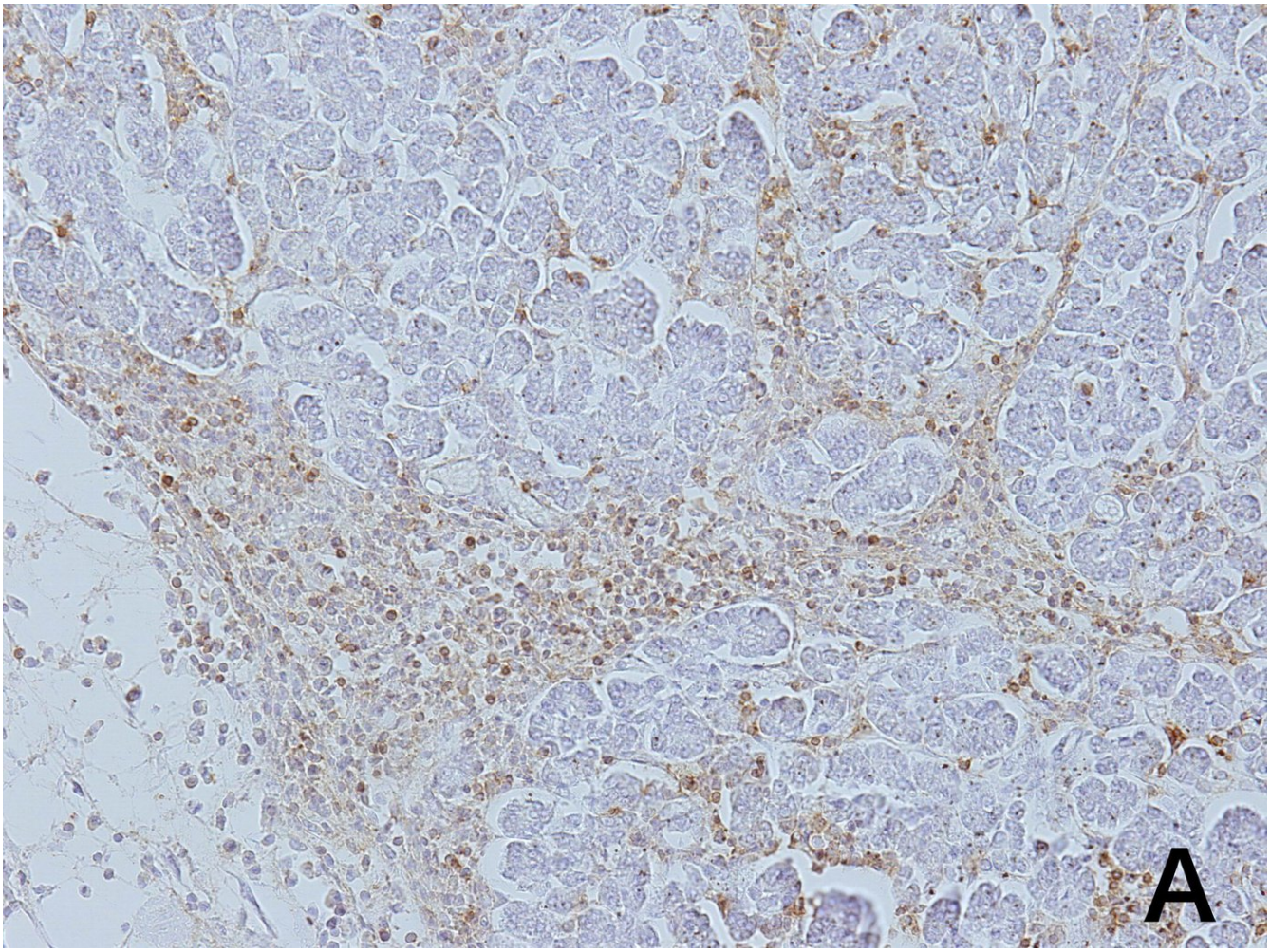
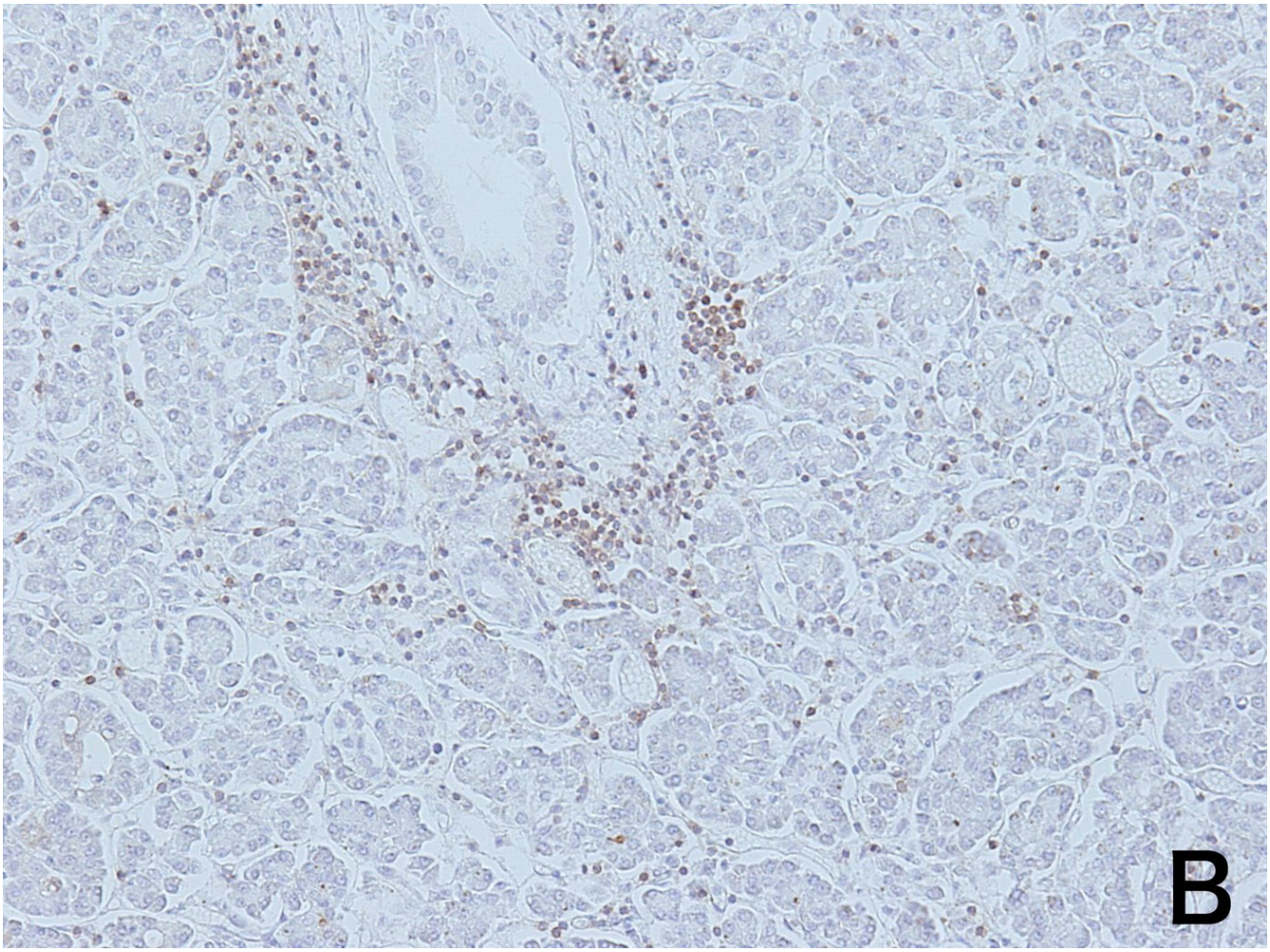
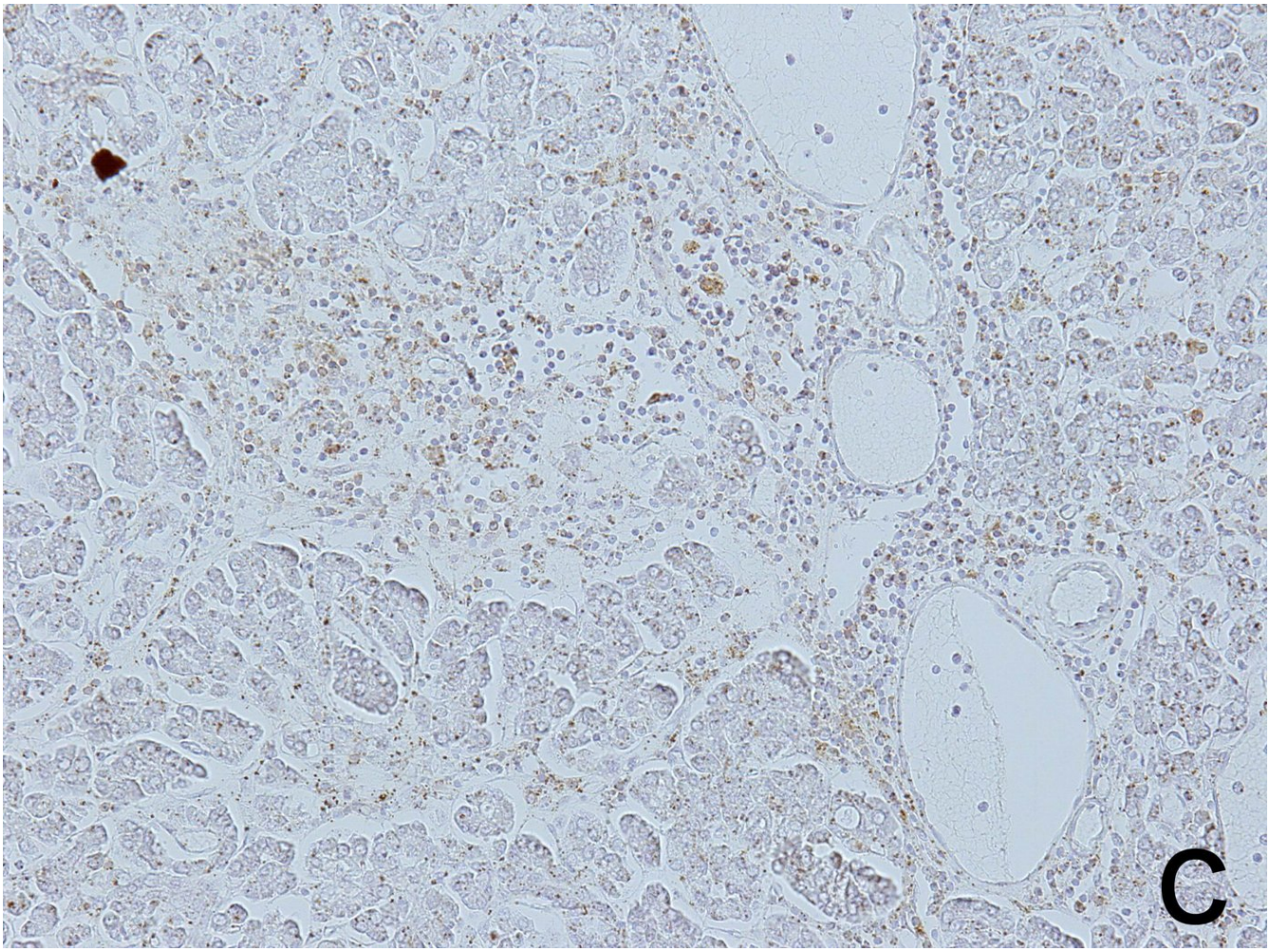


Figure 1. HE stains in the pancreas, the thyroid gland and the tonsil. Numerous lymphocyte were stained around the lobes of the pancreatic exocrine cells (1-A, top left), inter-spaces of colloidal cells of the thyroid gland (1-B, top right) and around the tonsil by HE stain (1-C, below left). The beta cells in the pancreatic islet were practically destroyed (1-D, below right). The infiltration manner of lymphocytes in the thyroid gland is different from that of Hashimoto disease.

Triage DOA (Sysmex) and rapid influenza diagnosis kit (Becton, Dickinson) showed no reactivity. Unfortunately HLA typing could not be examined. The autopsy findings and laboratory date combined with the symptoms speculated that he died of fulminant type 1 DM. Histological examination with HE staining showed the severe lymphocytes infiltration in the inter-space of exocrine cells of the pancreas, inter-space of the colloidal cells of the thyroid gland and around the tonsil as shown in Fig.1-A, 1-B and 1-C. Although the pancreatic islet cells were destroyed, lymphocytes infiltration of islet cells was not recognized (Fig.1-D).


A


B


C

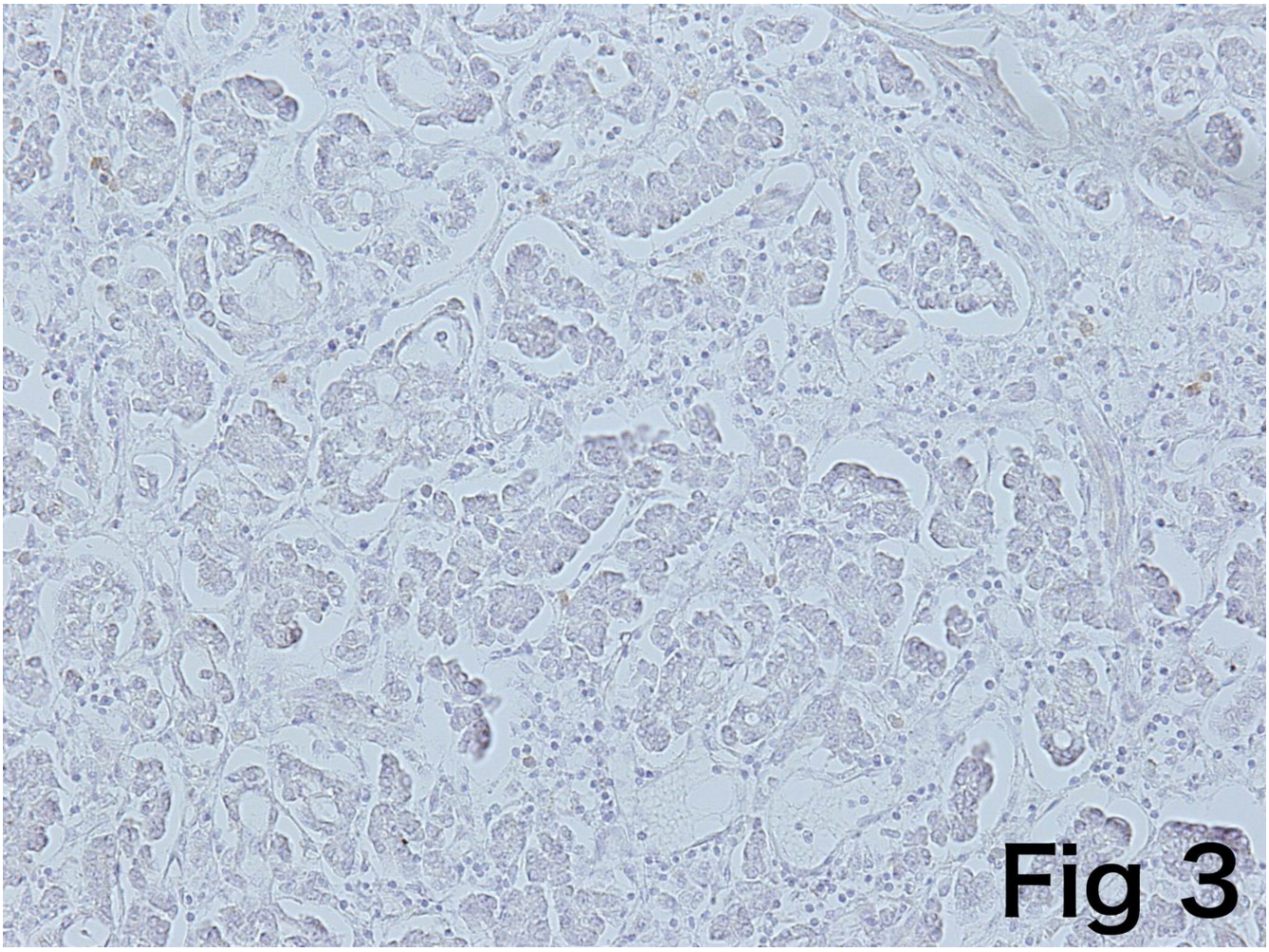


Figure 2. Staining results of the pancreas and with antibodies against surface antigens of lymphocytes, CD3, CD4 and insulin. Large amount of lymphocytes was observed around the lobes of pancreatic exocrine cells but not in islet cells (2-A, above left). Small amount of T cells were detected by anti CD3 or CD4 around the lobes of pancreatic exocrine cells but not in islet cells (2-B, above right and 2-C, below left). **Figure 3.** Staining results of the pancreas with anti-insulin antibody. No reactivity with anti-insulin was observed in the pancreas (below right).

Histological examination with HE stain also showed no diabetic findings in the kidneys, moderate fatty infiltration in the liver, small amount of fibrosis in the cardiac muscle, edematous change in the stomach and intestine, respectively. Immnohistochemical staining using antibodies against lymphocyte surface-antigens (Dako Japan), CD3 (Dako Japan) and CD4 (Dako Japan) showed that the lymphocytes contained many amount of T cells in the pancreas as shown in Fig 2-A, 2-B and 2-C. Anti-insulin antibody (Dako Japan) showed no reactivity with islet cells in the pancreas as shown in Fig.3. What is already known on this topic The fulminant type 1 diabetes mellitus was mainly observed in Asia, especially in Japan, but no case in Europe. However three patients were recently diagnosed in France. What This study adds There are few autopsy cases of fulminant type 1 diabetes mellitus. We did the histochemical examination for the first time. Suggestions for further development Biochemical analysis was available to decide the cause of death of the body. Since we had no pathological finding except edematous intestine and biochemical analysis indicated severe high glycemia. We should make histochemical and biochemical analysis at autopsies.

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Discussion

Type 1 DM is classified as autoimmune and idiopathic.[6] The committee of Japan Diabetes Society has proposed the following criteria for diagnosis of patients of fulminant type 1 diabetes mellitus: 1) development of ketosis or keto-acidosis within about one week after the appearance of symptoms of diabetes mellitus, 2) blood glucose of more than 288mg/dl and HbA1c less than 8.5% during the first examination, and 3) urinary CPR (C-protein) of less than 0.3ng/ml before glucagons stimulation and less than 0.5ng/ml after glucagons stimulation.[7]

A man in this report clinically fills the criteria described above. Although fulminant type 1 DM has been clinically recognized and reported mainly in Asia and no in Caucasians, [3,4,5] except three cases of French women,[8] the pathogenesis of the disease remains unclear. Individual relationships between diabetes mellitus with thyroid disease, viral infection and/or infiltration of T cells have long been recognized in the clinic. Since in this report the man showed T cell and lymphocyte infiltration in the pancreas and the thyroid gland, it is speculated that he has viral infection prior to development of hyperglycemia and keto-acidosis coma, and his immune reactivity could not fulfill within 1 week.

Although it remains to be resolved whether fulminant type 1 DM is caused by a shingle or multiple pathogenesis, the present case indicates that both of viral infection and T cell infiltration may play important roles in the development of fulminant type 1 DM. [9,10] It has been observing that the hyperglycemia is detected in the blood from the patients with hypothermia, acute stroke, subarachnoid hemorrhage, and/or septic or injury stress [11,12,13,14] The forensic pathologist should take notice of hyperglycemia in the performance of the autopsy, since the hyperglycemia decline the outcome of the patients. The laboratory analysis and histochemical examination were necessary at forensic autopsies.

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