Autoimmune Coagulation Factor X Deficiency as a Rare Acquired Hemorrhagic Disorder: A Literature Review

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Abstract

Coagulation factor X (F10) amplifies the clotting reaction in the middle of the coagulation cascade, and thus F10 deficiency leads to a bleeding tendency. Isolated acquired F10 deficiency is widely recognized in patients with immunoglobulin light-chain amyloidosis or plasma cell dyscrasias. However, its occurrence as an autoimmune disorder is extremely rare. The Japanese Collaborative Research Group has been conducting a nationwide survey on autoimmune coagulation factor deficiencies (AiCFDs) starting in the last decade; we recently identified three patients with autoimmune F10 deficiency (AiF10D). Furthermore, an extensive literature search was performed, confirming 26 AiF10D and 28 possible cases. Our study revealed that AiF10D patients were younger than patients with other AiCFDs; AiF10D patients included children and were predominantly male. AiF10D was confirmed as a severe type of bleeding diathesis, although its mortality rate was not high. As AiF10D patients showed only low F10 inhibitor titers, they were considered to have nonneutralizing anti-F10 autoantibodies rather than their neutralizing counterparts. Accordingly, immunological anti-F10 antibody detection is highly recommended. Hemostatic and immunosuppressive therapies may help arrest bleeding and eliminate anti-F10 antibodies, leading to a high recovery rate. However, further investigation is necessary to understand the basic characteristics and proper management of AiF10D owing to the limited number of patients.

Keywords
► coagulation
► factor X
► bleeding disorders
► autoantibodies
► nonneutralizing

Introduction

Coagulation factor X (F10) is one of the vitamin K (vit. K)–dependent coagulation factors and functions as an essential proenzyme in the common pathway. Its deficiency, either congenital or acquired in nature, leads to variable bleeding symptoms.[1,2]

As the number of patients with autoimmune coagulation factor deficiency (AiCFD) has been increasing in Japan, the Japanese Collaborative Research Group (JCRG) has been conducting a nationwide survey on this hemorrhagic disorder starting in the last decade.[3,4] Owing to this, autoimmune deficiencies of coagulation factors XIII (F13), VIII (F8), V (F5), and von Willebrand factor (VWF) have been approved as

designated intractable diseases (DIDs) with the code 288 by the Japanese Ministry of Health, Labor, and Welfare (MHLW). With respect to the order of prevalence, autoimmune F8 deficiency (AiF8D) is the most prevalent, followed by autoimmune F5 (AiF5D), F13 (AiF13D), and VWF (AiVWFD) deficiency; the cumulative numbers of the Japanese AiCFD cases are as follows: estimated 2,160 AiF8D cases and actual numbers of 173 AiF5D cases, 79 AiF13D cases, and 33 AiVWFD cases (JCRG's Achievement Report 2020 submitted to the Japanese MHLW).[4,5]

Autoimmune F10 deficiency (AiF10D) is less prevalent than the other AiCFDs, and thus, there were no records of physician consultations on AiF10D patients at the JCRG headquarters at Yamagata University during the first 7 years (2009–2017) of our survey. To the best of our knowledge, only nine AiF10D cases with F10 inhibitor involvement; six cases, suspected F10 inhibitor involvement; and 19 cases, no F10 inhibitor involvement have been reviewed in detail by Lee at al in 2012.[6]

Thus, we focused our search on AiF10D cases including F10 inhibitors during the past 3 years (2018–2020) and identified three new cases. In addition, we identified six cases of suspected AiF10D in Japanese individuals through periodic extensive literature searches of English and Japanese papers in the PubMed and Igaku Chuo Zasshi (ICHUSHI) databases, respectively. This article presents the clinical features of a total of 26 AiF10D patients, excluding 28 possible AiF10D patients, to improve the understanding and awareness of this disease.

Methods

Case Selection

The JCRG's survey and its special integrated/unified laboratory tests and our detailed experimental examinations were approved by Yamagata University's Institutional Review Board (IRB) as well as the IRBs of the individual hospitals to which each physician in charge of a patient belongs to. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

A typical bleeding patient initially visits a hospital, and the physician in charge of the patient consults with a hematologist, then the hematologist consults the patient with and/or reports her or him to the JCRG headquarters at Yamagata University (Yamagata, Japan). The patients' blood samples are collected and sent to a commercial laboratory (SRL Ltd., Hachioji, Japan) and the JCRG headquarters, separately.

We performed extensive literature searches at least twice a year in both the PubMed (in English) and ICHUSHI (in Japanese) databases. The search terms were as follows: ((((Acquired) OR (transient)) OR (temporary)) AND ((((((factor X)) OR (factor 10)) OR (Stuart factor)) OR (Power factor)) AND (deficiency))) NOT (((congenital) OR (hereditary)) OR (inherited)) for PubMed and similar Japanese terms for ICHUSHI.

The suspected AiF10D cases were selected by the diagnostic criterion previously proposed by the JCRG[4]: "definite"

diagnosis, when anti-F10 autoantibodies are detected in the patient's sample and "probable" diagnosis, when the sample is positive for an F10 inhibitor (termed as "probable-2" in this report) or when the 1:1 mixing test and/or cross-mixing test using the patient's and a healthy control's plasma samples (based on prothrombin time [PT] and/or activated partial thromboplastin time [aPTT]) presents an inhibitory pattern but not a deficient pattern in the presence of decreased F10 activity (F10:C; termed as "probable-1"). The remaining acF10D patients were included in a "possible" group. All congenital and other acquired F10 deficiencies (acF10Ds), such as vit. K deficiency, severe liver dysfunction, AL-amyloidosis (AL-Amyl), and plasma cell dyscrasia (PCD), as well as other AiCFDs, *were carefully excluded, as previously described by Lee et al.*[6]

Data Collection

The following data were collected from participating and reported patients: sex, age at presentation, bleeding symptoms, underlying diseases, hemoglobin concentrations, platelet counts, F10:C, F10 antigen (F10:Ag) levels, F10-specific activity (F10:C/Ag), anti-F10 autoantibody levels, F10 inhibitor levels, results of the mixing test based on PT and/or aPTT, PT, aPTT, fibrin/fibrinogen degradation products (FDPs), and D-dimer levels. In addition, clinical data, such as data on the use of hemostatic medicines and immunosuppressive agents, prognosis, and days to recovery (if recovered), were collected.

Statistical Analysis

Comparisons between the patients' groups were performed using the Pearson chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. Statistical analyses were performed using JMP software, version 12.2.0 (SAS Institute, Cary, North Carolina, United States). A p-value <0.05 was considered statistically significant.

For statistical purposes, F10:C or clotting times (PT, aPTT) less than or longer than the indicated values were considered as the indicated values, for example, $<1\%$ as 1% or >100 seconds as 100 seconds.

Results

Case Selection

During the past 3 years, five patients with suspected AiF10D consulted with the authors through the JCRG survey. Among them, three cases of AiF10D (two "definite" cases and one "probable" case) were identified based on the presence of anti-F10 autoantibodies and/or F10 inhibitors.[7–9] The remaining two suspected AiF10D cases were excluded because one patient was diagnosed with AL-Amyl based on the presence of amyloid deposition confirmed by biopsy and another patient was found to have AiF5D.

Our literature searches employing PubMed (last accessed on December 31, 2020) identified 208 reported cases and those employing ICHUSHI (last accessed on December 28, 2020) identified 39 reported cases (►**Fig. 1**). After excluding duplicates and cases of AL-Amyl and hereditary F10
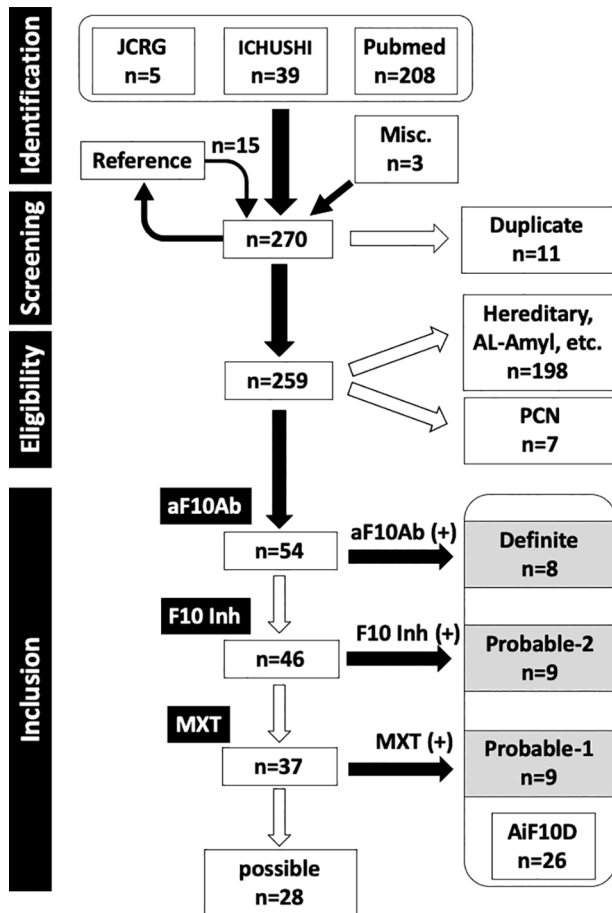
Fig. 1 Data selection flow. Patients were divided into four groups depending upon the presence or absence of an anti-F10 antibody (aF10Ab), F10 inhibitor (F10 Inh), or inhibitor pattern in mixing test (MXT) by PT and/or aPTT. AL-Amyl, light chain immunoglobulin amyloidosis; aPTT, activated partial thromboplastin time; ICHUSHI, Igaku Chuo Zasshi; JCRG, the Japanese Collaborative Research Group; Misc., miscellaneous; PCN, plasma cell neoplasm; PT, prothrombin time.

deficiency (F10D), a total of 54 suspected AiF10D cases were selected and classified into four subgroups: "definite" (8 cases), "probable-1" (9 cases), "probable-2" (9 cases), and "possible" diagnoses (28 cases; data not shown as requested by a section editor and a referee). One identified case was
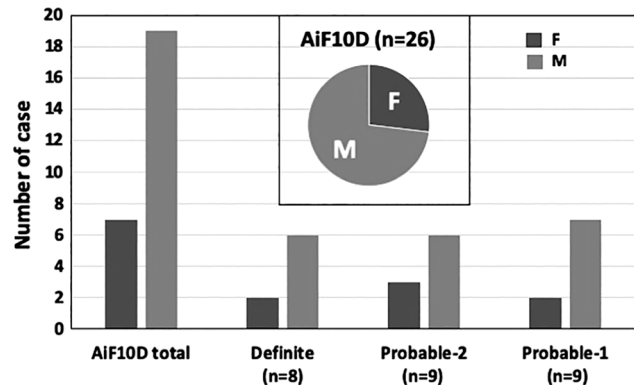

Fig. 2 Patient group and sex ratio in AiF10D cases. There were more male cases than females in the AiF10D group. Accordingly, the sex ratio (M/F) was higher than other AiCFDs. AiCFDs, autoimmune coagulation factor deficiencies; AiF10D, autoimmune F10 deficiency; F; female, M; male.

excluded because the patient had an autoantibody directed against multiple coagulation factors and his F10:C was 63%.[10] Two case reports were incidentally discovered.[11,12]

Seven patients with acF10Ds were separated into an additional subgroup of PCD, i.e., plasma cell neoplasms (PCNs), based on a previous study.[6]

Sex Ratio

The number of male patients was higher than that of female patients in AiF10D (►**Fig. 2**). The sex ratio (M/F) was high (2.7) and this value was inconsistent with the sex ratio (18/16 = 1.13) reported by a previous review in 2012.[6] This may be because our review included 12 additional patients with AiF10D involving F10 inhibitors, including eight newly diagnosed/reported cases after 2012. In addition, our review excluded 28 "possible" AiF10D patients while the previous review included 19 cases without F10 inhibitor.

Incidentally, the sex ratios in the AiF8D and AiF13D groups were 0.74 (52/70) and 1.21 (51/42), respectively.[13,14] The reason for the difference in sex predominance among AiCFDs is not known at present.

Age Distribution

The median age of AiF10D patients (59 years, $n = 26$; ►**Table 1**) was apparently lower than that of patients

Table 1 Age distribution in AiF10D cases

Group	Number	Mean ± SD	Median (IQR)	Range	p-Value
AiF10D					
Definite	8	61.1 ± 27.5	71.5 (81.8–40.8)	11–89	0.512[a] 0.312[b]
Probable-2	9	49.6 ± 27.0	58 (62–35)	1.5–90	
Probable-1	9	59.2 ± 11.7	59 (62–58)	34–77	0.451[c]
Total	26	56.5 ± 22.7	59 (70.5–44)	1.5–90	

Abbreviations: AiF10D, autoimmune F10 deficiency; IQR, interquartile range, SD, standard deviation.
Note: The differences were statistically insignificant.
[a]Definite vs. Probable-1.
[b]Definite vs. Probable-2.
[c]Probable-2 vs. Probable-1.

with other AiCFDs, such as AiF8D and AiF13D (median age: 78 years [range: 2–98 years; $n = 154$] and 70 years [range, 22–89 years; $n = 93$], respectively).[13,14] This is the most striking clinical feature of AiF10D compared with other AiCFDs; this difference may be due to the inclusion of two children with severe burns in the AiF10D group. Since most AiCFDs occur in elderly people, clinicians should pay attention when they encounter children with unexplained bleeding.

Underlying Diseases/Conditions

No underlying condition was found in 35% of all AiF10D patients (►**Supplementary Fig. S1**, available in the online version). Six AiF10D patients (25%) had infectious diseases (mainly involving the respiratory system), and two patients had leprosy. There were two cases of severe burns in the AiF10D group. The two patients with extensive burns were 1.5 and 11 years of age, and the two patients with leprosy were 18 and 35 years of age. This is the major reason why the mean age was lower in the AiF10D group than in the AiF8D and AiF13D groups, as described above. Antibiotics used for the treatment of infectious diseases may be related to the development of anti-F10 autoantibodies, as previously reported in the context of anti-F13 autoantibodies.[14]

Nevertheless, AL-Amyl is the most important disease for the differential diagnosis of AiF10D because it is characterized by an acF10D together with the concomitant prolongation of PT and/or aPTT[15,16]; the bleeding symptoms are worse in patients with the lowest F10 levels.[16,17] As the previous review excluded not only AL-Amyl but also other PCDs,[6] we classified seven patients with monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma (MM) into a PCN group. In general, quite a few patients with MGUS show progression to plasma cell myeloma (including MM), and patients with MGUS and MM frequently develop AL-Amyl[18–21] (►**Supplementary Fig. S2**, available in the online version). The authors of two of the seven case reports hypothesized that the causes of acF10D in their patients were related to AL-Amyl, although amyloid deposits were not identified on biopsy.[22,23] What surprised us most was that one of the seven separated cases turned out to be the same patient as a chronic lymphocytic leukemia case published 10 years after original reports,[24,25] who afterward demonstrated the direct deposition of F10 onto amyloid in autopsy specimens.[26] This is in good agreement with the fact that asymptomatic AL-Amyl is present at the time of diagnostic bone marrow biopsy in newly diagnosed patients with MM and smoldering myeloma.[27] In addition, it is likely that some AL-Amyl patients are being overlooked.[21,28] It is thought that the excess light chains produced by the myeloma clone bind the circulating F10,[1] as deposited amyloid fibrils do.[26,29]

Bleeding Sites/Symptoms and Bleeding Severity

Most AiF10D patients showed bleeding in soft tissue regions, such as subcutaneous tissues (65%), the intestines (62%), and the urinary tract (52%) (►**Fig. 3**). Neither splenic nor intraperitoneal bleeding was reported in AiF10D cases, in contrast to that in AiF8D and AiF13D cases.[13,14] However, three
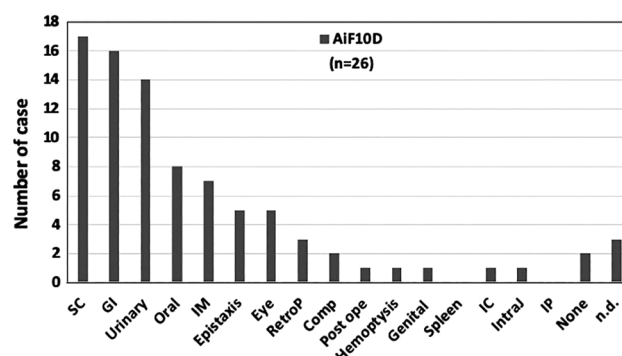

Fig. 3 Bleeding sites/symptoms in AiF10D cases. Many patients had more than one bleeding sites and/or symptoms. The AiF10D group experienced 87 bleeding symptoms/sites in total (3.35 per patient on average). AiF10D, autoimmune F10 deficiency; Comp, compartment syndrome; GI, gastrointestinal; IC, intracranial; IntraJ, intrajoint; IM, intramuscular; IP, intraperitoneal; n.d., not described; Post ope, postoperation; RetroP, retroperitoneal; SC, subcutaneous.

AiF10D cases were complicated by retroperitoneal bleeding. Only two AiF10D cases (8%) were devoid of bleeding symptoms.

When we applied the published categories of clinical bleeding severity,[30] it was noted that as many as 70% of AiF10D patients showed Grade III bleeding (►**Supplementary Fig. S3A**, available in the online version), indicating that this disease may be more severe than congenital F10D[2] (only 23.5% of patients experienced Grade III bleeding).[30] Incidentally, 22% of patients in the AiF10D group demonstrated Grade II bleeding.

The AiF10D group demonstrated intramuscular bleeding frequently (7 cases). Two AiF10D patients also developed compartment syndrome.

Concomitant Prolongation of PT and aPTT and a Decrease in F10 Activity

The mean hemoglobin concentration in the AiF10D group was 7.6 ± 1.8 g/dL (median: 7.6 g/dL, $n = 17$; ►**Table 2**, top). The platelet count was within reference range.

Both PT and aPTT were considerably or extremely prolonged in the AiF10D group (►**Table 2**, top), indicating abnormalities in factors in the common pathway of the coagulation cascade.

As expected, F10:C was severely reduced in the AiF10D patients (►**Table 2**, middle). This may be associated with the relatively severe bleeding tendency in AiF10D, as observed in congenital F10D.[1,2] However, there was no clear correlation between F10:C levels and the severity of bleeding symptoms (►**Fig. 4A**), consistent with that reported previously.[6] Similarly, F10:C levels did not correlate with hemoglobin levels (►**Fig. 4B**) that reflect the severity of bleeding.[31] In fact, four AiF10D cases manifested grade III, III, III, and II bleeding symptoms, although they had considerable levels of F5 activity (13, 16, 19, and 25%, respectively).[32–35] F10:C levels did not correlate with any of F10 inhibitor titer, PT, or aPTT (►**Fig. 4C–E**), while PT and aPTT did show a statistically significant correlation ($p < 0.0001$; ►**Fig. 4F**).

Although the number of samples was limited, the F10:Ag level varied from normal levels to extremely reduced levels

Table 2 Routine and coagulation tests in AiF10D cases

Test item	Number	Mean ± SD	Median (IQR)	Range
Hemoglobin (g/dL)	17	7.6 ± 1.8	7.6 (8.8–6.4)	12.0–5.2
Platelet (×10^{10}/L)	17	30.1 ± 11.7	24.6 (40–20.7)	53–14.5
PT (s)	26	74.6 ± 60.7	65.5 (100–27.5)	300–13.5
aPTT (s)	25	84.6 ± 37.2	79.0 (103.2–51)	200–40.5
F10:C (%)	26	5.7 ± 6.5	3.5 (9–1)	25–0
F10:Ag (%)	4	45.2 ± 50.3	32.5 (71.3–6.4)	111–4.6
F10:C/Ag	4	0.3 ± 0.2	0.3 (0.4–0.2)	0.6–0.1
Fibrinogen (mg/dL)	19	436 ± 125	435 (527.5–327.5)	641–210
FDP (μg/mL)	3	8.0 ± 19.6	11.6 (25.8–7.1)	40–2.5
D-dimer (μg/mL)	7	1.5 ± 1.7	0.5 (1.7–0.4)	4.2–0.25

Abbreviations: AiF10D, autoimmune F10 deficiency; aPTT, activated partial thromboplastin time; F10:Ag, F10 antigen; F10:C, F10 activity; F10:C/Ag, F10-specific activity; FDPs, fibrin/fibrinogen degradation products; IQR, interquartile range; PT, prothrombin time; SD, standard deviation.

in AiF10D patients. Thus, the specific activity of F10 (F10:-C/F10:Ag, F10:C/Ag) was quite low in the AiF10D group. This is consistent with the idea that at least some F10 molecules are inhibited by neutralizing anti-F10 antibodies, i.e., an F10 inhibitor, resulting in the formation of an antigen–antibody complex. This leads to a reduction in the specific activity of F10 in AiF10D patients, as discussed later.

The F10 inhibitor titer was determined only in eight AiF10D cases: the values were 5.4, <0.4, 0, 1, 1.6, <1, 0, and 0 BU/mL. Only one patient showed a high titer (>5 BU/mL) in the AiF10D group; in contrast, AiF8D or AiF13D patients frequently show high titers.[13,36] This is also a striking difference between AiF10D and other AiCFDs.

Test results on lupus anticoagulant (LA) were reported in 11 AiF10D patients; negative in 4 AiF10D cases, positive in 6 patients,[6,8,32,37,38] and unmeasurable in 1 case.[7] Anticardiolipin and/or anti-β$_2$-glycoprotein antibodies were negative in four out of the seven LA-positive or unmeasurable cases,[6–8,32]
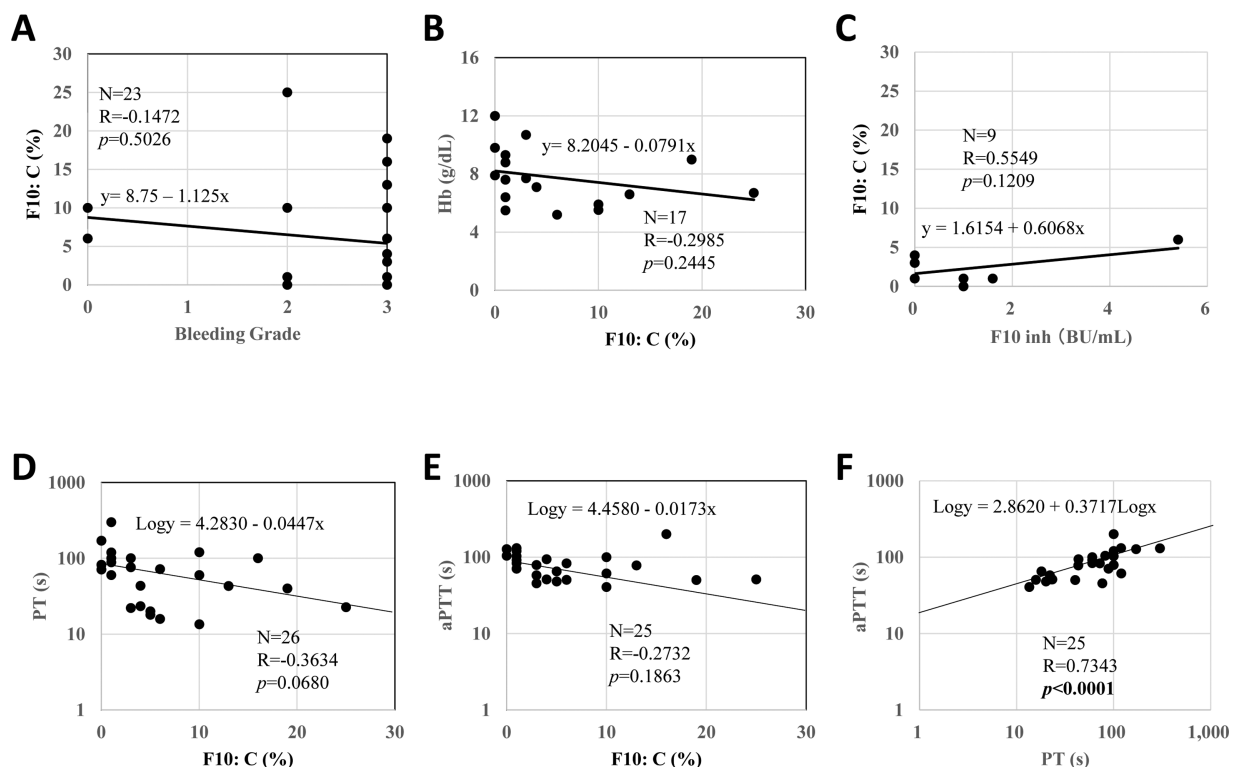

Fig. 4 Relationship between F5 activity and bleeding severity (A), hemoglobin levels (B), and other parameters (C–F) in AiF10D cases. (A) There was no significant correlation between F10:C levels and the severity of bleeding symptoms, i.e., Grades 0, I, II, and III (p = ns). (B–E) Similarly, F10:C levels did not correlate with any of hemoglobin levels, F10 inhibitor titer, PT, or aPTT. (F) PT and aPTT did show a statistically significant correlation. Grades 0, I, II, and III are shown as 0, 1, 2, and 3. AiF10D, autoimmune F10 deficiency; aPTT, activated partial thromboplastin time; PT, prothrombin time.

while anticardiolipin antibody was positive in only one patient.[38] LA was confirmed to have disappeared in three cases after immunosuppressive therapy[8,32,37] and in one case spontaneously,[37] while the fate of anticardiolipin antibody of two cases was not described.[6,38] In addition, the unmeasurable LA became measurable and was negative in one case after immunosuppressive therapy.[7] Thus, it is likely that LA in most of these cases was pseudopositive or transient, because they were an isolated severe F10D due to specific F10 inhibitors, and their LA did not last more than 12 weeks, both situations of which did not meet the criteria of LA.[39–42]

Anti-F10 Autoantibodies

The presence of anti-F10 autoantibodies has been detected only in eight AiF10D patients.[7,8,32,34,35,43–45] In five of these cases, the anti-F10 autoantibodies were identified to be of the immunoglobulin G class. It should be noted that two patients had anti-F10 autoantibodies that were calcium-dependent binding antibodies, and thus, it is reasonable to presume that these antibodies inhibited the functional clotting activity of F10. However, the specimen from one patient did not show potency for F10 inhibition,[45] while that from the other patient did.[32] Therefore, the former patient seemed to have nonneutralizing autoantibodies against F10. This was also true in one of our patients, who showed an extremely low F10:C level (<1%) in the absence of an F10 inhibitor.[7] *It should be emphasized that all patients suspected of having AiF10D should be immunologically examined for anti-F10 autoantibodies because functional F10 inhibitor assays are unable to detect nonneutralizing autoantibodies against F10.*

Accordingly, it is likely that at least some of the 28 patients in the "possible" group may have had nonneutralizing autoantibodies against F10 because they also showed extremely low F10:C levels in the absence of an F10 inhibitor.

Fibrinolytic Parameters

Fibrinogen levels varied widely in the AiF10D group (►**Table 2**, bottom). FDPs and D-dimer levels were slightly–moderately elevated in several cases, probably reflecting bleeding events and/or consequent hematomas.

FDP and D-dimer levels were reported for only a limited number of patients: three and seven cases in the AiF10D group, respectively. These parameters may be particularly important for excluding AL-Amyl from the differential diagnosis because patients with AL-Amyl demonstrate moderately elevated FDP and D-dimer values.[17,46]

Fibrinolytic and coagulation parameters, i.e., such as plasmin–α_2-plasmin inhibitor complex (PIC) and thrombin–antithrombin (TAT) complex, were reported to be important for recognizing a hyperfibrinolytic state and a hypocoagulation state, respectively, in bleeding patients with AL-Amyl.[17,46,47] However, PIC and TAT complexes were measured in only 1 of the 26 AiF10D cases,[8] although these parameters may be highly useful for differentiating AiF10D from AL-Amyl.

Hemostatic Treatment

Hemostatic therapy was reported in 23 out of 26 AiF10D cases (►**Fig. 5A**). Fresh frozen plasma (FFP) and vit. K were
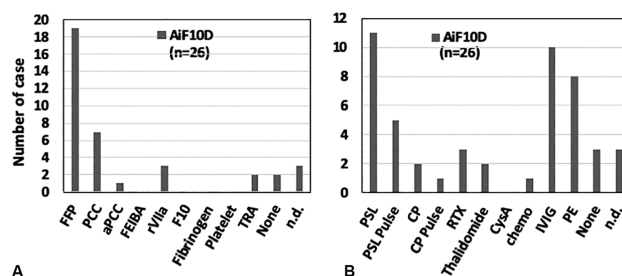
Fig. 5 Hemostatic (A) and antibody eradication/reduction (B) therapies in AiF10D cases. (A) Fresh frozen plasma (FFP) was most frequently administered to AiF10D patients, followed by prothrombin complex concentrates (PCCs). (B) Prednisolone (PSL) was most frequently used in the AiF10D cases in high doses or pulse administration. Cyclophosphamide (CP) was given to them in regular or very high (pulse) doses. These patients underwent high-dose intravenous immunoglobulin (IVIG) and plasma exchange (PE) treatments. AiF10D, autoimmune F10 deficiency; aPCC, activated PCC; chemo, chemotherapy; CysA, cyclosporine A; F10, factor X/10; FEIBA, factor eight inhibitor bypassing activity; n.d., not described; rVIIa, activated recombinant factor VII; RTX, rituximab; TRA, tranexamic acid.

administered to 73 and 61% of AiF10D patients, respectively. FFP was not very effective in arresting bleeding, probably because it contains only 1 U/mL of F10, and repeated administration may be risky in AiF10D patients with ongoing bleeding because of possible circulatory overloading (given at the most 59 units).[7] Alternatively, prothrombin complex concentrates (PCCs) were used in 27% of AiF10D patients as these products contain more F10 for inducing hemostasis.[48] Vit. K had little or no effect on the patients' bleeding, confirming that vit. K deficiency is not the cause of bleeding in AiF10D patients. Antifibrinolytic agents, such as tranexamic acid, were used in only 8% of all AiF10D patients. This may be because AiF10D patients did not show a hyperfibrinolytic state, unlike AL-Amyl patients, as discussed above. No hemostatic medicine was administered in 8% of AiF10D cases, mainly because these patients did not show any bleeding symptoms.[49]

A high-purity plasma-derived F10 concentrate has been developed by a British company,[50] which may be more effective than PCCs for inducing hemostasis in patients with various types of F10D because it contains greater amounts of F10 and lesser amounts of other vit. K-dependent factors. Unfortunately, this product is not currently available in Japan. Instead, a Japanese company developed a plasma-derived product containing both activated factor VII/7 (F7a) and F10 (10 times of F7a) for the treatment of hemophilia with alloantibodies (e.g., F8 inhibitors).[51] It will be administered for treating any F10D, regardless of hereditary or acquired origin, in the near future.

Regarding the adverse effects of using hemostatic products, it is important to note that an AiF10D patient experienced multiple cerebral infarctions 2 to 3 days after the cessation of PCC administration.[52]

Antibody Eradication/Reduction Therapy

In total, 42% of AiF10D patients initially received prednisolone (PSL) for antibody eradication (►**Fig. 5B**), consistent

Table 3 Time to recovery (days) in AiF10D cases

Group	Number	Mean ± SD	Median (IQR)	Range	p-Value	
AiF10D						
Definite	8	29.6 ± 13.8	29 (39–19)	50–13	0.520[a]	0.233[b]
Probable-2	4	19.5 ± 8.4	21 (23.5–17)	28–8		
Probable-1	7	25.6 ± 21.2	13 (47–7.5)	50–7		1.000[c]
Total	19	26.0 ± 15.8	22 (40.5–13)	50–7		

Abbreviations: AiF10D, autoimmune F10 deficiency; IQR, interquartile range; SD, standard deviation.
Note: The differences were statistically insignificant.
[a]Definite vs. Probable-1.
[b]Definite vs. Probable-2.
[c]Probable-2 vs. Probable-1.

with the autoimmune origin of AiF10D. Similarly, a pulse PSL regimen was employed in 19% of AiF10D cases. Rituximab, an anti-CD20 monoclonal antibody, and cyclophosphamide were used in 12 and 8% of AiF10D cases, respectively.

Patients in the AiF10D group were treated with high-dose intravenous immunoglobulin therapy and plasma exchange (PE): 38 and 4% of patients in the AiF10D group. However, with respect to antibody reduction, physicians should remember that the effect of PE is theoretically transient in nature. None of the patients underwent antibody adsorption therapy.

Prognosis

Outcomes were reported in 21 of 26 AiF10D cases (►**Supplementary Fig. S3B**, available in the online version). Sixty-nine percent of patients achieved full resolution, and one showed partial resolution. No patients were reported to show spontaneous resolution.

In contrast to the previous review,[6] this review described mortality related to AiF10D. Of the 26 AiF10D patients, two patients died due to retroperitoneal hemorrhage and renal failure (female, 50 years of age)[53] and sepsis (male, 59 years of age).[33] The death of the former patient may be attributable to hemorrhage.

F10D contributed to death in at least one AiF10D case (4%). When compared with those in patients with other AiCFDs, the rate of hemorrhagic death was not high in patients with AiF10D, despite them being severe bleeding disorders, as discussed above.

To the authors' best knowledge, no relapse has been reported in the AiF10D group. The mean time to recovery was 26.0 ± 15.8 days in the AiF10D group (►**Table 3**).

Limitations

There are several limitations to our study: (1) the number of patients was too small because of the rarity of this disease; therefore, it was difficult to draw any conclusion regarding first-line therapy as well as long-term prognosis. (2) As we tried to collect as many AiF10D cases as possible, we included one AiF10D patient whose case was reported in an abstract form alone. (3) Seven acF10D cases involving PCNs were separated from the AiF10D group, because MGUS, MM, and AL-AML are closely related to each other. (4) The mechanism of AiF10D was not explored as it was beyond the scope of the present review.

To overcome some of these limitations, the JCRG has started the use of a database-based registry system, named the Japanese DID platform (use started on February 1, 2021). This system will allow us to conduct long-term follow-up, to clarify the patients' prognosis precisely, and to establish the optimal first-line and second-line therapies for AiF10D.

Conclusion

This review provides the most comprehensive knowledge regarding AiF10D to date: (1) The mean age at onset is lower than that for other AiCFDs; even children can develop AiF10D. (2) A male predominance was confirmed in our present study. (3) AiF10D is one of the most severe types of hemorrhagic diseases. (4) AiF10D patients had rather low F10 inhibitor titers, suggesting the presence of nonneutralizing and hyperclearance-type anti-F10 autoantibodies. (5) As nonneutralizing anti-F10 autoantibodies can be overlooked in functional F10 inhibitor assays, immunological anti-F10 antibody detection is highly recommended. (6) The hemorrhagic death rate is not higher than expected (based on the severe bleeding tendency). (7) Owing to its high recovery rate, the prognosis of AiF10D seems fairly good.

When an actively bleeding patient demonstrates concomitant prolongation of PT and aPTT without personal and family history of bleeding diathesis and anticoagulant dosing, as well as extremely low F10:C regardless mixing test based on PT and aPTT is positive or negative, a physician(s) in charge of the patient should suspect AiF10D. Because AiF10D can be caused by both or either neutralizing and/or nonneutralizing types of anti-F10 autoantibodies, both F10 inhibitor and anti-F10 autoantibodies should be examined to certainly diagnose AiF10D[4] (Diagnostic Criterion 2019 for AiF10D [in English]).

Finally, we hope that this review will help and encourage clinicians who face challenges in diagnosing and treating patients with AiF10D.

Author Contributions

A.I. initiated and designed the study, extracted data, wrote, edited, and proofread the manuscript. T.O. conducted experimental examinations, statistical analyses, and proofread the manuscript. M.S. performed experimental examinations, and proofread the manuscript.

Conflict of Interest

None declared.

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