Japanese Journal of Transfusion and Cell Therapy, Vol. 68. No. 1　68(1)：12—16, 2022

—【Case Report】— 症例報告 —

A case of severe pain and redness at the puncture sites for blood transfusion —Acute localized pain transfusion reaction?

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Acute pain transfusion reaction (APTR) is a rare adverse event (AE), characterized by severe pain in the trunk and extremities accompanied by dyspnea, hypertension and chills soon after initiation of a transfusion. It disappears after stopping the transfusion. We experienced a case of severe pain and redness that was limited to the puncture sites.

The patient had received a stent graft for acute aortic arch dissection six months before presentation. At our hospital he received another stent graft and underwent an artery bypass operation, in which autologous red blood cells (RBCs) were transfused without incident. On the following day, one bag of pre-storage leukocyte- reduced RBCs (PLR-RBCs) derived from 400 m*l* of whole blood was transfused. Immediately after initiating the transfusion, severe pain and redness at the puncture site occurred. The transfusion was stopped, and the symptoms disappeared approximately 10 minutes later. When the same blood was transfused into the opposite arm, similar symptoms with a temporary slight increase in blood pressure (BP) occurred and disappeared after stopping the transfusion. Hemolytic findings were not detected. Two more PLR-RBCs bags were thereafter administered without AEs. On the second day, when one PLR-RBCs bag was transfused, the same symptoms appeared and disappeared after stopping the transfusion.

These AEs with severe pain and redness at the puncture sites without other symptoms except a temporary slight increase in BP, might be due to a form of acute localized pain transfusion reaction (ALPTR) distinct from APTR.

Keywords: pain transfusion reaction, transfusion adverse event, leukocyte reduced red blood cells

Introduction

Acute pain transfusion reaction (APTR) is a rare adverse event (AE). It involves severe pain in the trunk and proximal extremities within 30 minutes after transfusion initiation and disappears within 30 minutes after stopping the transfusion. It is associated with systemic symptoms including dyspnea/tachypnea, hypertension, chills, headache and flushing[1)2)]. However, localized findings at the puncture sites have not been described. We experienced a case of severe pain and redness that was limited to the puncture sites and systemic symptoms limited to a temporary slight increase in blood pressure (BP).

Case presentation

The patient was a 68-year-old man. His blood type was B, RhD positive without irregular antibodies. He had a history of polyarteritis nodosa and hypertension treated with a calcium channel blocker and a β-blocker. However, he had no history of transfusion or of allergic reactions to food, drugs or contrast medium. In January 2017, he experienced a backache and was diagnosed with acute aortic arch dissection (Stanford-B). He received a thoracic aortic stent graft without transfusion. In July 2017, he developed a pseudoaneurysm at the graft site. He received another chest stent graft and underwent a bilateral axillary artery bypass operation, in which 635 m*l* of salvage autologous red blood cells (RBCs) using a cell saver was transfused without AEs.

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〔Received: June 30, 2021, Accepted: December 7, 2021〕

On the following day after the operation, his hemoglobin (Hb) was 8.1 g/d*l*, and one bag of prestorage leukocyte-reduced red blood cells (PLR-RBCs 1, 15 days old) derived from 400 m*l* whole blood, compatible with routine cross-match tests, was transfused. Severe pain and redness without itching or swelling around the puncture site occurred immediately after initiation of the transfusion, and disappeared approximately 10 minutes after stopping the transfusion. When the same blood was transfused into the opposite arm after a 10-minutes interval, similar symptoms accompanied by a temporary slight increase in BP (117/74 to 132/72 mmHg) were observed 15 minutes after starting the transfusion. The symptoms disappeared 10 minutes after stopping the transfusion. Two more bags (i.e., PLR-RBCs 2 [12 days old] and PLR-RBC 3 [9 days old]) were then administered without AEs. On the second postoperative day after the operation, his Hb was 8.7 g/d*l*, and PLR-RBCs 4 (12 days old) was transfused. Immediately after initiation of the transfusion, severe pain within area of erythema 5 cm in diameter developed at the injection site, accompanied by a temporary increase in BP (145/72 to 160/74 mmHg) without other systemic symptoms. These symptoms disappeared 5 minutes after stopping the transfusion.

Laboratory findings before/after PLR-RBCs 1 transfusion of total bilirubin (0.7/1.0 mg/d*l*, normal range [NR: 0.5～1.5 mg/d*l*]), LDH (264/240 U/*l*, NR: 124～222 U/*l*) and AST (19/15 U/*l*, NR: 13～30 U/*l*) are shown in Table 1, 2. No clerical errors of ABO mismatched transfusion of PLR-RBCs 1 such as wrong blood samples or mistaken records were detected. Anti-HLA antibodies were not examined.

Leukocyte-reduction filters (LRFs) used for PLR-RBCs 1, PLR-RBCs 2 and PLR- RBCs 4 at the Japanese Red Cross Blood Center (JBC: Tokyo, Japan) were manufactured by the same company (Table 3). The LRFs for PLR-RBCs 3 was manufactured by a different company. All the transfusion sets of four blood bags used for transfusion were produced by the same company.

Discussion

The clinical time course of pain in our patient-pain occurring within 20 minutes after initiating transfusion, then disapperaring 10–20 minutes after stopping the transfusion-was similar to that reported in previous APTR cases[1)2)]. Characteristically, the pain in APTR oc-

Table 1　Hematological findings

	7/28 (pre-op.)	7/31 (post-op.)	8/1 (post-op. day 1)	8/2 (post-op. day 2)
WBC ($\times 10^3/\mu l$)	6.2	7.1	18.9	16.1
RBC ($\times 10^6/\mu l$)	4.11	3.47	2.72	2.86
Hb (g/d*l*)	12.1	10.3	8.1	8.7
Hct (%)	37.9	31.6	25.4	25.1
PLT ($\times 10^3/\mu l$)	84	56	75	79
PT-INR	1.04	1.18	NT	1.00
APTT (sec.)	34.5	NT	NT	32.2
Fib. (mg/d*l*)	161	NT	NT	NT
CRP (mg/d*l*)	0.66	0.29	5.55	10.70

cf. NT: not tested

Table 2　Biochemical findings

	7/28 (pre-op.)	7/31 (post-op.)	8/1 (post-op. day 1)	8/2 (post-op. day 2)
TP (g/d*l*)	7.0	5.2	5.2	5.5
Alb (g/d*l*)	4.2	3.0	3.1	3.4
T-Bil (mg/d*l*)	0.7	1.0	1.0	1.0
Na (mmol/*l*)	141	140	142	140
K (mmol/*l*)	3.8	3.8	4.8	3.9
CL (mmol/*l*)	107	109	108	107
CK (U/*l*)	59	109	142	203
AST (U/*l*)	19	15	18	17
ALT (U/*l*)	8	6	7	7
LD (U/*l*)	264	240	235	269
BUN (mg/d*l*)	14.2	16.2	29.0	42.8
CRE (mg/d*l*)	0.87	0.94	1.80	1.69

Table 3　Manufactures (T, K, J, A and F) of blood bags and leukoreduction filters, and storage days of 4 PLR-RBCs transfused according to presence or absence of adverse events.

	Adverse Events (+)		Adverse Events (−)	
	PLR-RBCs1	PLR-RBCs4	PLR-RBCs2	PLR-RBCs3
Blood Bag	T	T	K	J
Leukocyte reduction filter	A	A	A	F
Storage days	15	12	9	12

cf.　PLR-RBCs: prestorage leukocyte-reduced red blood cells. Number 1 through 4 of PLR-RBCs indicates the order of transfusions.

curs in the trunk and proximal extremities, but there has been no description of the pain at the puncture site. Our patient had pain limited to the puncture sites with no systemic symptoms except for a temporary slight increase in BP. This AE might be named "acute localized pain transfusion reaction (ALPTR)", to distinguish it from APTR.

In a summary report of AEs associated with transfusion in Japan[3], vascular pain is associated with hemolytic transfusion reactions. Our patient did not have hemolytic transfusion reactions, based on the lack of hemolytic laboratory findings and clerical errors, In one report[4)5)], only the number of patients with vascular pain, is mentioned (e.g., 21 cases of RBCs transfusion and one case of platelet concentrates [PCs] transfusion in 2016, and 21 cases of RBC transfusion in 2017). It would be difficult to distinguish between previously reported cases with vascular pain and those with ALPTR, because it would not be clear whether cases with vascular pain were associated with redness at the infusion sites. If they could be investigated in more detail, some of them might be ALPTR. In the AE report from JBC[6], there were no incidents of pain with transfusion. In the SHOT report[7], one case of presumed APTR was described as a rare case but lacked a description of the puncture site, and another case of APTR was reported, in which there was no description of the puncture site[8].

The causes of ALPTR and APTR are unknown. However, a correlation with leukoreduction filters (LRFs)[1)2)9)] or anti-HLA antibodies[1)10)] has been suggested for APTR. Since January in 2007, JBC has manufactured and supplied PLR-RBCs using LRFs for all whole blood. However, there are no reports of AEs similar to our case. The LRFs used for PLR-RBCs 1 and PLR-RBCs 4 (i.e., AEs) and PLR-RBCs 2 (i.e., non-AEs) were manufactured by the same company (Table 3). A case of APTR following PCs transfusion without leukoreduction filtration[1)] and a case of following packed RBCs transfusion[9)] have been reported. Thus, the occurrence of ALPTR due to LRFs is not necessarily due to leukocyte reduction filtration. Transfusion sets can be excluded as the cause, because transfusion sets of the same lot were used for the transfusion of the four blood bags. Moreover, the presence of anti-HLA antibodies is hard to predict: our patient was a man and had no history of transfusion in his past history, although he was not tested for anti-HLA antibodies. Polyarteritis nodosa would be unlikely to be the cause of ALPTR, because this is a disease of arteries and blood is usually transfused into veins.

A recent report speculated that some cytokines associated with pain, especially IL-1β, TNF-α, IL-6 and IL-8, might cause APTR due to packed RBC transfusion[9)].

In previously reported APTR associated with leukoreduction filtration, which would be presumed to be used at time of transfusion[1)2)9)], the amount of cytokines produced by leukocytes would be almost the same as that in packed RBCs (Number of leukocytes in order of 10^{11}/bag). This might suggest cytokines as a cause of ALPTR. Although leukocytes in PLR-RBCs in our case were $<10^{6}$/bag (validated in more than 95% of PLR-RBCs[11)]), much less than the number in packed RBCs, some PLR-RBCs bags might contain $>10^{6}$ leukocytes. The small amount of cytokines produced by the leukocytes could cause ALPTR without systemic symptoms but not APTR. On the other hand, pain at the infusion site in hemolysis may be the result of rapid complement activation, which produces cytokines[12)]. Two PLR-RBCs bags associated with ALPTR in our case were 15 and 12 days old, which could include a number of hemolyzed RBCs below the threshold but plentiful enough to activate complement for production of cytokines without systemic symptoms.

However, it would be hard to explain why these cytokines would not show pain around puncture sites in APTR with systemic symptoms, and why APTR or ALPTR has been reported so rarely. This suggests that the grade of pain would be from very severe in our case (ALPTR), to very mild, to be overlooked in APTR with severe systemic symptoms. Factors other than cytokines need investigation.

Conclusion

We reported here a case of rare AEs occurring immediately after initiation of transfusion, including severe pain and redness limited to the puncture sites and no systemic symptoms other than a temporary slight increase in BP, which we are calling ALPTR to distinguish it from APTR. Since ALPTR might be underreported, physician should keep these AEs in mind when a patient has a reaction to a blood transfusion.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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輸血穿刺部位に見られた激痛と発赤を伴った急性輸血反応 ―急性局所疼痛性輸血反応？

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要旨：

急性疼痛性輸血反応（acute pain transfusion reaction；APTR）は，輸血開始後 30 分以内に躯幹や四肢近位部に疼痛を認め，中止後 30 分以内に消退し，呼吸困難，血圧上昇，悪寒，頭痛，潮紅などを伴う稀な副反応であるが，穿刺局所の疼痛や発赤の記載はない．我々は，激痛と発赤が穿刺部位に限局し，軽度の血圧上昇以外の症状を認めない症例を経験した．

症例は，68 歳男性で，輸血歴はない．2017 年 1 月急性解離性弓部大動脈瘤でステンドグラフト術を受けた．7 月再度ステントグラフト術と両腋窩動脈間バイパス術を受け，術中回収式自己血は副反応なく輸血し得た．翌日，同型適合貯留前白血球除去赤血球液（prestorage leukoreduced RBCs； PLR-RBCs）の輸血開始直後より穿刺部位の激痛と発赤を認め，中断 10 分後に症状は消退した．別腕で同製剤を再輸血したが，同様な症状と一過性の軽度血圧上昇を認め，中断した．溶血所見は認められなかった．その後，他の 2 バッグの PLR-RBCs 輸血は副反応なく行いえた．翌々日，同型適合 PLR-RBCs の輸血開始後に同様な症状と一過性の軽度血圧上昇を認め，中断 5 分後には症状は消退した．

この急性輸血副反応は，激痛と発赤が穿刺部位局所に限られ，一過性の軽度血圧上昇以外の症状を認めないことから，APTR とは異なる急性局所疼痛性輸血反応（acute localized pain transfusion reaction；ALPTR）と称するのが妥当ではないかと考えられる．

キーワード：
疼痛性輸血反応，輸血副反応，白血球除去赤血球液

Journal Web Site: http://yuketsu.jstmct.or.jp/