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Donor Follow-Up of Influenza Vaccine-Related Multiple Viral Enzyme Immunoassay Reactivity

Abstract

False-positive enzyme immunoassay (EIA) tests in blood donors receiving influenza vaccine were first reported in 1991. We conducted follow-up testing for 6 months of those donors with multiply reactive, but unconfirmed EIA (at least 2 positives in anti-HCV-1.0, anti-HIV-1, and anti-HTLV-I assays) with a history of recent flu vaccine to determine the duration of false positivity. Of 133,000 donors tested, 16 met study criteria: all 16 were reactive for anti-HCV, 10 were reactive for anti-HIV-1, and 12 were reactive for anti-HTLV-I. Fifteen donors were available for follow-up testing (using the original screening and supplemental tests): 10 (67%) reverted to negative for the 3 tests and 5 remained false positive for various markers at last sampling (3-6 months after vaccination). The mean duration of false positivity for those reverting to negative EIA test status, was 4.2 months (range 2-7 months) indicating a transient phenomenon and supporting studies which suggest a role for IgM in the mechanism.

Introduction

When unanticipated multiply reactive, but unconfirmed viral enzyme immunoassay (EIA) activity was first observed in blood donors with recent history of influenza vaccination in late 1991, there was confusion for donors and adverse publicity for blood collection programs [1]. In this study we examined the persistence of multiple, unconfirmed repeatedly reactive viral EIA test results in donors with recent history of influenza vaccination. It was felt that specific data regarding the natural history of the test abnormality might provide useful information for donor management.

Methods

Health history records were reviewed for vaccination status in all donors whose serum tested repeatedly reactive, but unconfirmed, in multiple viral EIA assays from September 1991 through March 1992 at the Northeast and Atlanta Regions of the American Red Cross Blood Services. Multiple EIA unconfirmed reactivity was defined as an unconfirmed, but repeatedly reactive result in at least two of the following tests: anti-HIV-1, anti-HCV, and anti-HTLV-I. Those donors who reported having received influenza vaccinations within the past year were contacted for one or more follow-up samples. Samples were retested using the same test-of-record and supplemental tests. All screening tests were conducted using Abbott reagents (Abbott Laboratories, Abbott Park, Ill., USA) for anti-HIV-1, anti-HCV (1st generation), and anti-HTLV-I. Confirmatory testing for anti-HIV-1 was done by Western blot, for anti-HCV by RIBA-2, and for anti-HTLV by

Table 1. Persistence of EIA reactivity following influenza vaccine

Donor ID	Interval after influenza vaccine, weeks													
	1	2	3	4	6	8	11	13	15	17	19	21	26	30
3-MR08				HCV HTLV										NEG
3-MR07										HCV HTLV			NEG	
3-MR09				HCV HTLV									NEG	
3-MR04				HCV HTLV								NEG		
3-MR02		HCV HTLV	HCV HTLV								NEG			
4-MR17						HIV HCV HTLV		NEG						
4-MR14	HIV HCV HTLV			HCV				NEG						
4-MR16			HIV HCV				NEG							
4-MR12	HIV HCV						NEG							
3-MR01				HIV HCV HTLV	HCV	NEG								

The dark shading indicates the persistence of EIA-reactive results for tests noted.
The lighter shading indicates negative EIA screening results for all 3 viral tests.

Western blot and specific EIA HTLV-I and HTLV-II if indicated (note that in March 1992 anti-HIV-1 and anti-HCV were replaced by anti-HIV-1/2 and anti-HCV 2.0, respectively, at Red Cross Blood Services). We were able to obtain follow-up samples from 94% of study subjects. There was a wide range of intervals between samples in some cases.

Results

During the influenza inoculation season spanning September to December of 1991, 75,326 Northeast Region and 57,817 Atlanta Region whole blood and plateletpheresis

collections were made for a total of 133,143 donations. Of these, there were 16 donors (0.012%) in whom a history of influenza vaccine and multiple unconfirmed EIA reactivity was found. Of the 16 donors with multiple unconfirmed EIA reactivity, 13 (81%) were male and 3 (19%) female. The mean age at time of donation was 45 years (range 18-73). Twelve of the donors had made previous donations and there were two autologous donors. The mean interval from time of vaccination to index donation was 1.4 months (range 1 week to 4 months). All donors were EIA repeatedly reactive for anti-HCV. Ten were repeatedly reactive for anti-

Table 2. Persistence of EIA reactivity following influenza vaccine

Donor ID	Interval after influenza vaccine, weeks													
	1	2	3	4	6	8	11	13	15	17	19	21	26	30
4-MR11	HIV HCV													
4-MR15		HIV HCV HTLV			HIV HCV HTLV				HCV					
4-MR19						HIV HCV	HCV		HCV					
3-MR03				HIV HCV						HIV				
3-MR05								HIV HCV HTLV	HIV HCV HTLV	HIV HCV HTLV				
3-MR06										HCV HTLV			HCV	

The shading and tests noted indicate the persistence of EIA reactivity for donors who did not revert to negative during the follow-up period.

HIV-1 and 12 were repeatedly reactive for anti-HTLV-I. Five donors were positive for all three markers.

Of the 16 donors, 15 were available for at least one follow-up. During the time of our study, the serum of 10 donors had reverted to entirely EIA negative (67%), while 3 remained EIA repeatedly reactive/RIBA negative for anti-HCV (20%), and 1 remained EIA repeatedly reactive/Western blot negative for anti-HIV (6.5%). In only 1 sample did the EIA reactivity for all three markers (6.5%) persist (at 4 months following the index donation).

Of the donors reverting to EIA-negative test status, the range for reversion was 2–7 months (table 1). It must be noted that since timing between the index donation and the follow-up sample collection was uncontrolled, there was a wide range of intervals between collections and it is impossible to pinpoint the time of reversion from reactivity to negative test status. However, assuming that reversion took place just prior to sample collection (the maximum case), the average duration of reactivity was 4.2 months.

For the donors who remained test positive during the study (table 2), the maximum known periods were 6 months for 1 anti-HCV-reactive individual and 3.5–4 months for 4 donors with various combinations of the three markers. Un-

fortunately, we were unable to contact these donors for continued follow-up testing as they had moved from the area or were autologous donors who declined further testing.

Discussion

Based on these findings, it appears that multiply unconfirmed viral EIA reactivity in blood donors associated with the 1991–1992 influenza vaccination is a temporary phenomenon. On average the abnormality can no longer be identified at a mean of 4.2 months after administration of the influenza vaccine. These findings are consistent with those recently published by MacKenzie et al. [2]. These investigators found that after a mean follow-up of 75 days, 6 of 6 donors studied had reverted to negative reactivity for HIV-1, 5 of 6 donors reverted to negative for HTLV-I but only 3 of 7 donors available for HCV follow-up reverted to negative status.

An explanation for this phenomenon has been found during the past year in studies of Stramer et al. [3], Holzer et al. [4] and Wieblen et al. [5]. They have shown that a small percentage of vaccine recipients (1–2%) have a nonspecific

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IgM response to the inoculation. This IgM apparently binds to any polystyrene surface of the test kit (bead or microtiter plate). Those test kits which use a conjugate containing antibodies to human IgM light chain may exhibit cross-reactivity with any bound IgM on the test surface. Variability of cross-reactivity is seen from manufacturer to manufacturer and from test to test. As each manufacturer refines their conjugates for optimal sensitivity and specificity, this cross-reactivity may increase or decrease; therefore, new kits may show an increased or decreased susceptibility to this phenomenon.

The EIA Abbott HIV-1/2 and Ortho HCV 2.0 test kits which were introduced in the spring 1992 both have conjugates which appear to have eliminated this nonspecific IgM cross-reactivity. As anti-HCV reactivity was the most frequent abnormality, we retested all 16 of the originally reactive donor aliquots using Ortho Diagnostics (Raritan, N.J., USA) anti-HCV 2.0, the current test-of-record. Using this assay, every sample was anti-HCV EIA negative. In addition, we have not seen any multiple unconfirmed EIA positivity over the last year at our centers but we have seen another seasonal increase in HTLV EIA-reactive/Western blot-negative donors with a recent history of influenza vaccination, with similar observations being noted in *Morbidity and Mortality Weekly Report* [6].

Our study concentrated on the duration of the unconfirmed reactivity. The average time of 4.2 months for those donors reverting to negative test results and the maximum persistence of reactivity seen at 6 months fall within the expected guidelines for IgM antibody duration. Although we are no longer seeing multiple reactivity, false reactivity still occurs in our HTLV test.

We emphasize the need to review influenza vaccination status in implicated donors. They should be counseled and be reassured that their health is not affected. With regard to donor reentry, we recommend that once reactivity to viral screening tests has disappeared they should be reinstated. It is hoped that by providing affected donors with more definitive information regarding these influenza vaccine-related findings, including an accurate estimate of the abnormality's persistence, their confidence in the blood collectors will be restored.

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