Significance of cytomegalovirus infection in the failure of native arteriovenous fistula

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Abstract

High cytomegalovirus (CMV) IgG levels have been identified as a risk factor for arteriovenous fistula (AVF) failure. None of the 68 patients in our study were CMV IgM positive, although 96% were CMV IgG positive. CMV antigens were detected in the radial artery or cephalic vein of 46% of patients who received an AVF. The presence of CMV antigens or high serum CMV IgG levels had no prognostic value for AVF failure.

Keywords: Arteriovenous fistula, cytomegalovirus, dialysis, stenosis, thrombosis

Original Submission: 16 June 2011; Revised Submission: 14 September 2011; Accepted: 30 September 2011

Editor: L. Kaiser

Article published online: 5 October 2011

Clin Microbiol Infect 2012; 18: E5–E7
10.1111/j.1469-0691.2011.03691.x

Cytomegalovirus (CMV), a member of the herpesviridae family, establishes latency after primary infection, is reactivated by inflammation and can sustain an inflammatory response [1]. Based on its pro-inflammatory properties, CMV is believed to mediate the development of various vascular diseases [1,2]. CMV has been detected in abdominal aortic aneurysm [3,4], atherosclerosis and transplant vascular sclerosis [2,5]. High anti-CMV IgG levels also have predictive value for coronary heart disease [6], and for all-cause and cardiovascular mortality [7,8]. Noteworthy is that several studies have been unable to confirm the presence and potential role of CMV in these conditions [5,9–12].

Native arteriovenous fistula (AVF) is the preferred form of haemodialysis access but because of dysfunction it also remains a major cause of morbidity in these patients [13]. Failure of AVF is predominantly the result of venous stenosis and thrombosis; AVF patency rates at 2 years after construction are approximately 75%, when fistulae that fail to mature adequately to support haemodialysis are excluded [14]. Although numerous risk factors for AVF failure have been identified, they do not explain all the AVF failures [15]. High anti-CMV IgG levels have been identified as an independent risk factor for haemodialysis access thrombosis [16,17]. We examined the CMV IgG and IgM levels, and the presence of CMV proteins in the vessels and their effects on AVF outcome.

In this prospective study, 68 patients with end-stage renal disease who received a native haemodialysis AVF at the Department of General, Vascular and Oncologic Surgery, Central Clinical Hospital Ministry of Internal Affairs, Warsaw, Poland, between 1 June 2006 and 30 September 2007 were included. The patients were aged 62 ± 15 (mean ± SD) years at the time of surgery, and 46 (68%) were men. They were followed for 24 months or until AVF failure, the study endpoint. Informed consent was obtained from all patients, and the ethical committees at Karolinska Institutet (2011/411-31/1) and at the Central Clinical Hospital Ministry of Internal Affairs (40/2005) approved the study. The AVF failure rate at 24 months was 50% in this population, of which 15% was as a result of primary failure, consistent with previous observations [18].

The CMV serological status (IgG and IgM) of the patients was determined before surgery using an automated analyser and the Liaison CMV IgG and IgM assays (DiaSorin, Saluggia, Italy). All patients were CMV IgM negative, whereas 65 (96%) were CMV IgG positive, with titres ranging between 1.7 and >22 IU/mL. Three patients (4%) were CMV IgG negative (levels <0.2 IU/mL), and their fistulae functioned for 3–6 months after surgery. The patient population was divided into tertiles for subsequent analysis, based on serum CMV IgG levels (first tertile: <0.2 to 9.2 IU/mL, second tertile: >9.2 to 17.0 IU/mL, third tertile: >17 to >22 IU/mL). Patency rates of the AVF were analysed using Kaplan–Meier curves and evaluated by log-rank test. Higher CMV IgG titres were not associated with lower durations of AVF function (p = 0.52) (Fig. 1).

The radial artery and cephalic vein biopsies that were obtained at the surgical creation of AVF were stained for CMV immediate early (IEA) and late (LA) antigens by immunohistochemistry as described previously [3]. Briefly, following deparaffinization and blocking, sections were stained with
antibodies against CMV IEA and LA (both from Chemicon International, Temecula, CA, USA), and alpha smooth muscle actin (BioGenex, San Ramon, CA, USA), which was used as a control; followed by staining with a secondary biotinylated antibody and streptavidin-conjugated horseradish peroxidase (both from BioGenex). The antigens were visualized using the chromogen diaminobenzidine (Innovex Biosciences, Richmond, CA, USA).

The CMV IEA/LA were detected in the radial arteries of 38% of patients evaluated but were present in only 19% of the cephalic veins evaluated. In the majority of biopsies, a few scattered CMV-positive cells were observed, and the CMV proteins were expressed predominantly in inflammatory cells (Fig. 2a,b). To determine the potential prognostic value of the presence of CMV proteins in the vessels, Kaplan–Meier curves were constructed for the patients with and without CMV vessel antigens. The curves were compared using the log-rank test. No significant difference in AVF failure rate was noted between the groups (p = 0.85) (Fig. 2c).

High CMV IgG serum levels, which have been associated with AVF failure in two studies, had no predictive value for AVF failure in our study. In the retrospective case–control study by Grandaliano et al. [16], a defined cut-off that corresponded to approximately the top 17% of CMV IgG population levels was used, versus the cut-off set corresponding to approximately the top 13% of CMV IgG population levels used by Gagliardi et al. [17]. Further, CMV serology was not evaluated before AVF construction in these studies, and neither study examined the presence of CMV in the affected vessels.

Solely serological approaches are problematic, because CMV antibody titres can fluctuate tremendously through repeated reactivation of latent infections. Any association between AVF failure and CMV IgG levels measured at a specific time-point will be substantially weaker than associations of AVF failure with average CMV IgG levels over longer periods or with the presence of CMV at the anatomically relevant site [5].

Notably, although we detected CMV proteins in the vessels of 46% of the patients at the time of surgery, the presence of CMV proteins was not predictive of AVF failure. Our results do not fully exclude CMV as a potential contributor to AVF failure, and it is possible that CMV activity is triggered at a later stage, potentially contributing to AVF failure. Further prospective studies that evaluate consecutive serum samples for CMV IgG and examine vessels at the time

**FIG. 1.** No significant differences were observed in arteriovenous fistula (AVF) patency rates in patients with high cytomegalovirus (CMV) IgG levels. First tertile: <0.2 to 9.2 IU/mL, second tertile: >9.2 to 17.0 IU/mL and third tertile: >17 to >22 IU/mL.

**FIG. 2.** Cytomegalovirus (CMV) protein-positive cells (brown) were found in the radial arteries of 38% of the patients evaluated while they were present in only 19% of the cephalic veins of the patients evaluated (IEA, immediate early antigen) (a). Alpha smooth muscle actin (α-SMA) was used as a positive control (b). Presence of CMV antigens in the vessels does not have prognostic value for arteriovenous fistula (AVF) patency (c).
of construction and failure are warranted to fully address the potential role of CMV in AVF failure.

Acknowledgement

We thank Fredrik Hansson for advice on statistical analysis.

Transparency Declaration

This work was supported by the Science Research Committee MNiSW grants 2 P05C 010 30 and PBZ/MEiN/01/2006, the Swedish Heart-Lung Foundation, the Swedish Research Council, Karolinska Institutet, the Foundation for Geriatric Research, Stiftelsen Gamla Tjänarinnor and the Swedish Society of Medicine. M.D. is supported by the Karolinska Institutet MD/OD-PhD programme.

C. S.-N. holds an investigational grant from Roche to investigate the effects of antiviral treatment in glioblastoma multiforme. C. S.-N. has received speaker’s fees from Roche for basic science lectures on CMV pathology. The authors have declared that no conflict of interest exists.

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