19 Transplantation of Solid Organs, Tissues, and Prosthetic Devices in Patients with Antiphospholipid Antibodies

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Historical Prospective

References to transplantation are found in Greek mythology and in legends and folk tales of the Middle Ages. The first clinical report of a successful transplant was by Bunger in 1823, after he reconstructed a woman's nose by using tissue from her thigh [1]. In the ensuing decades, the success of skin and kidney transplantation was a very controversial topic wherein some investigators reported certain successes whereas others observed only failures [1]. It was not until the age of modern transplantation immunology ascribed to the work of Nobelist Sir Peter Medawar in the 1940s that transplantation became feasible [1]. The foundation for clinical transplantation was established soon after when Murray and colleagues successfully transplanted a kidney from one twin into his identical brother [2]. With these foundations, the ability to successfully transplant tissues and organs became a major medical achievement of the second half of the 20th century.

Advancements in surgical techniques, development of improved immune modulating pharmaceuticals, and a clearer understanding of the immune system vis-à-vis histocompatibility, rejection reactions, and tolerance induction have contributed to ever increasing success rates for solid organ and tissue transplantation. Despite these gains, a small but significant number of allografts fail immediately or within the first weeks after transplant. A frequent observation in these early allograft failures is localized vascular thrombosis within the grafted tissues.

First described in 1969 by Colman and coworkers, immediate thrombosis of renal allografts was suspected to be a result of acute rejection or of an immunologically induced coagulopathy [3]. The thrombosis was limited to the allograft as there was no evidence to suggest systemic coagulation or fibrinolysis. This localization suggests that allografted tissue provides not only a trigger but also a confined location for thrombosis. A literature search using *transplantation* and *thrombosis* as key words revealed reports of thrombosis associated with almost every transplanted organ or tissue with the exception of the cornea. This may not be surprising inasmuch as the cornea is avascular. Indeed, even the transplantation of autologous tissues has been associated with thrombosis [4].

Thromboembolic complications after transplantation have been associated with inherited thrombophilic disorders including deficiencies of antithrombin, protein C and protein S, factor V Leiden, the prothrombin G20210A and MTHFR C585C gene mutations, and dysfibrinogenemias [5, 6]. Acquired disorders associated with transplant related thrombosis include antiphospholipid antibodies (aPL), malignancy, myleoproliferative disorders, heparin-induced thrombocytopenia, and hyperhomocysteinemia. This chapter will confine discussion to a review of aPL in the transplantation literature as it relates to aPL.

aPL Testing

Before proceeding with this review, several points about aPL testing need be brought to the reader's attention. First, publications associating aPL with allograft thrombosis begin in 1988, 20 years after numerous reports showing allograft loss due to thrombosis. Second, assays for aPL are still evolving; functional tests for detection of lupus anticoagulant (LA) were available prior to the solid phase aPL ELISA systems. Standardization efforts continue for both aPL detection assays. Unfortunately, in many of the papers reviewed for this chapter, the LA and ELISA methodologies are omitted or are only partially described, making it difficult to accurately combine patient populations to make broader conclusions. The methodology and reagents used for aPL ELISA testing can have a profound effect on the test result [7]. ELISA procedures that do not consider the presence or absence of known phospholipid (PL)-binding plasma proteins can furnish false negative aPL findings [8]. Assays which use diluent buffers that contain only β_2-glycoprotein I ($ß_2$-GPI) will not detect aPL, which are dependent upon other PL binding proteins such as prothrombin or protein C. Third, the aPL ELISA is not standardized, thus the criteria for defining aPL positivity can vary between laboratories. For example, some laboratories limit aPL analyses to IgG and IgM anticardiolipin (aCL) as available in commercial kits. Other laboratories also include analysis of IgA aCL. In contrast, our laboratory ELISA is designed to detect all three antibody isotypes for aCL as well as antibodies with additional PL specificities, including antiphosphatidylserine (aPS), antiphosphatidylethanolamine (aPE) and antiphosphatidylcholine (aPC). Finally, as aPL can be associated with subclinical as well as clinical infections; it has been recommended that a patient with a positive aPL finding be retested 6 to 8 weeks later. It is important to discriminate between chronic and temporary presence of aPL, the former thought to be pathogenic, whereas the latter may not be. Few retrospective transplant studies tested serial blood samples from the same patient, however, when serial samples were tested aPL were found in multiple samples.

Analyses of our own data from 5632 consecutive serum samples from patients with aPL associated clinical events revealed that that testing for only IgG and IgM aCL underestimates the number of patients who have aPL [9]. IgA aPL can, and often does, occur independent of IgG and IgM. Further, we observed a significant incremental increase in aPL-positive sera when aPS and aPE are assessed in addition to aCL. Table 19.1 shows the incremental increase of aPL positivity when aPC testing was included in the analysis of 1758 clinical specimens referred for aPL testing. Thus, the aPL findings reported in the majority of the papers cited in this