absorption on to tumour cell lines, low pH dissociation of active serum samples, and subsequent antibody tests or titration studies with soluble tumour extracts, since it is known that C1q binding activity decreases in antigen excess.[18] In animal studies our findings and those of others[19] show that low levels of immune complexes have to be interpreted in the light of the patient's clinical state, since a significant drop in detectable serum immune complexes occurs in animals with a large tumour burden shortly before death. This probably reflects a shift in antigen-antibody balance to high antigen excess. Thus, low levels of C1q binding activity can occur when no tumour is left or a large tumour burden is present.

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BK antibody and virus-specific IgM responses in renal transplant recipients, patients with malignant disease, and healthy people

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Summary

Haemagglutination-inhibition (HAI) antibodies to BK virus, including BK-virus-specific IgM, were determined before and after renal transplantation in 20 patients, in 57 patients with malignant disease, and in 66 healthy controls. Before transplantation 11 of the renal transplant recipients were seronegative, but eight later seroconverted, two before and six after transplantation. Twenty of the patients with malignant disease and 22 controls were also seronegative. The geometric mean titre of BK HAI antibodies was significantly higher among transplanted patients (1/180) than among controls (1/90). BK-virus-specific IgM antibody was detected in seven renal transplant recipients, six patients with malignant disease, and 13 healthy controls.

In transplant recipients BK-virus-specific IgM antibody usually persisted throughout the duration of the study, and studies on controls from whom second serum samples were available suggested that they too had persistent BK-virus-specific IgM responses. The geometric mean titre of BK-virus-specific IgM HAI antibody was significantly greater in post-transplantation sera (1/223) than in control sera (1/28). The specificity of the detection of BK-virus-specific IgM HAI antibody was confirmed by direct visualisation of antibody by immune electron microscopy. The persistence of BK-virus-specific IgM suggested that BK virus continued to provide an antigenic stimulus. Nevertheless, there was no obvious association between the serological findings and any clinical features, and prospective studies will be needed to elucidate any such association.

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Introduction

BK virus was originally isolated from the urine of a patient after renal transplantation[1] and is a member of the papova group of viruses. Antibodies to this virus are common in the general population, and serological studies suggest that primary infection often occurs in childhood.[2-5] In England 37% of children have BK antibody by the age of 5 and this proportion has increased to 73% by the age of 10; a similar proportion of adults are also seropositive.[2] Nevertheless, BK virus has been recovered only from immunocompromised patients,[6-8] and virus recovery or seroconversion has not as yet been associated with any clinical features. This suggests that after primary infection BK virus may persist in a latent form but be reactivated in immunocompromised patients.

Some persistent infections in man may be associated with prolonged virus-specific IgM responses.[9-15] Although BK-virus-specific IgM may be detected in patients who have had renal transplantation,[16] it is not known whether it also occurs in other groups of immunocompromised patients or in apparently

healthy people with pre-existing BK-virus haemagglutination-inhibition (HAI) antibodies. We therefore compared serological responses to BK virus, including tests to detect virus-specific IgM in patients undergoing renal transplantation, in patients with malignant disease treated with cytotoxic drugs, and in apparently healthy controls.

Subjects and methods

Serial serum samples were collected from 20 patients at St Thomas's Hospital at varying intervals before and after they underwent renal transplantation. Patients' immune responses were suppressed after transplantation by treatment with azathioprine and corticosteroids. Single serum samples were collected from 57 patients with malignant disease who were being treated at St Thomas's Hospital with a regimen of prolonged chemotherapy, which included cytotoxic drugs and corticosteroids. These patients included 10 with Hodgkin's disease, 10 with myelomatosis, 10 with chronic lymphatic leukaemia, 10 with carcinoma of the breast, 13 with non-Hodgkin's lymphoma, and four with ovarian carcinoma. Sera were also obtained from 66 apparently healthy local authority and hospital employees who acted as age- and sex-matched controls.

HAI TESTS

BK-virus antigen was prepared in Vero cell cultures,[1] and HAI tests were carried out according to the method described by Gardner.[2]

DETECTION OF BK-VIRUS-SPECIFIC IGM

A 0·2-ml serum sample was pretreated with 0·8 ml receptor-destroying enzyme and incubated for 18 hours at 37°C. To obviate the heat aggregation of IgG that occurs at 56°C,[17] sera were inactivated at 46°C for 30 minutes and then fractionated on sucrose density gradients at 100 000 *g* for 18 hours.[18] Each 0·5-ml serum fraction was tested at a starting dilution of 1/2 for HAI antibodies to BK virus, fractions being incubated with 8-16 BK HA units for 18 hours at 4°C. Fractions were regarded as negative if there was no inhibition in the first dilution. Fractions were also tested by single radial immunodiffusion to ensure that IgM had clearly separated from IgG and IgA. IgM fractions containing HAI antibody were tested for sensitivity to 2-mercaptoethanol[19]; a reduction of at least fourfold in antibody titre was regarded as significant, and further tests for specificity were carried out by immune electron microscopy.

IMMUNE ELECTRON MICROSCOPY

BK virus—Virus was purified by treatment with Arcton 113,[20 21] ultrasonicated, and concentrated by centrifugation at 35 000 *g* for two hours. The pellet was resuspended in distilled water and used at a dilution providing an approximate virus particle count of 30 per grid square. Virus preparations and either IgM- or IgG-containing fractions were reacted together in unit volumes of 0·025 ml in microtitre U-bottom plates for one to two hours at room temperature and then left overnight at 4°C. Fractions were tested undiluted or at dilutions of 1/4 or 1/8. Preparations were then negatively stained with 3% phosphotungstic acid (pH 6·5) and examined with a Philips 201C electronmicroscope.

SV40 virus—A purified preparation of SV40 virus was obtained from Dr A Smith (Imperial Cancer Research Fund, London) and was used at a dilution which provided an approximate virus particle count of 30 particles per grid square. Immune electron microscopy was carried out as described above for BK virus.

Results and comment

Eleven of the 20 patients in the renal transplant group were seronegative. Eight of these patients developed significant rises in BK HAI antibody titres and may therefore have experienced primary BK-virus infections. Two had developed HAI antibodies by the month before transplantation and six developed them two days to seven months after transplantation. Nevertheless, three patients, one of whom had been transplanted twice, remained consistently seronegative throughout the study, their sera being collected over intervals ranging from five to 25 months. Two patients who received renal transplants were returned to haemodialysis during the second month after transplantation. One of these patients developed a rise in BK antibody while on haemodialysis.

Twenty of the 57 patients with malignant disease and 22 of the 66 controls were seronegative. The geometric mean antibody titres were higher in renal transplant recipients than in patients with malignant disease or controls (table I). Nevertheless, only the difference between post-transplantation titres and titres among controls was statistically significant ($0{\cdot}02 > P > 0{\cdot}01$).

TABLE I—*HAI antibodies (reciprocal titres) in renal transplant recipients, patients with malignant disease, and controls*

	Transplant recipients		Patients with malignant disease	Controls
	Before	After		
No of subjects	20	20	57	66
No (%) seronegative	11 (55)*	3 (15)	20 (35)	22 (33)
Range of titre	<40–1280	<40–10 240	<40–5120	<40–2560
Median titre	26	126	119	70
Geometric mean titre	50	180	115	90

*Two patients seroconverted before transplantation.

Both patients who seroconverted before transplantation and four of the six who seroconverted afterwards, including one of the patients who was returned to haemodialysis, developed BK-virus-specific IgM. In addition, one patient with a titre of 1/80 before transplantation developed a significant rise ($1/\geqslant 10\ 240$) two months after transplantation. BK-virus-specific IgM was absent from the pretransplantation serum but present in the post-transplantation sample. The two patients in whom BK-virus-specific IgM was not detected developed only low levels of BK antibody (1/40). Once detected, BK-virus-specific IgM antibody persisted in all but one of the patients who underwent renal transplantation. The one exception was the patient who returned to haemodialysis.

BK-virus-specific IgM was detected in seven of the 20 patients who underwent transplantation, six of the 57 patients with malignant disease, and 13 of the 66 controls (19·7%), all BK-virus-specific IgM-positive sera being sensitive to 2-mercaptoethanol. BK-virus-specific IgM titres in the patients who had undergone transplantation were significantly higher ($0{\cdot}01 > P > 0{\cdot}001$) than those in controls but not significantly different from those in patients with malignant disease (table II).

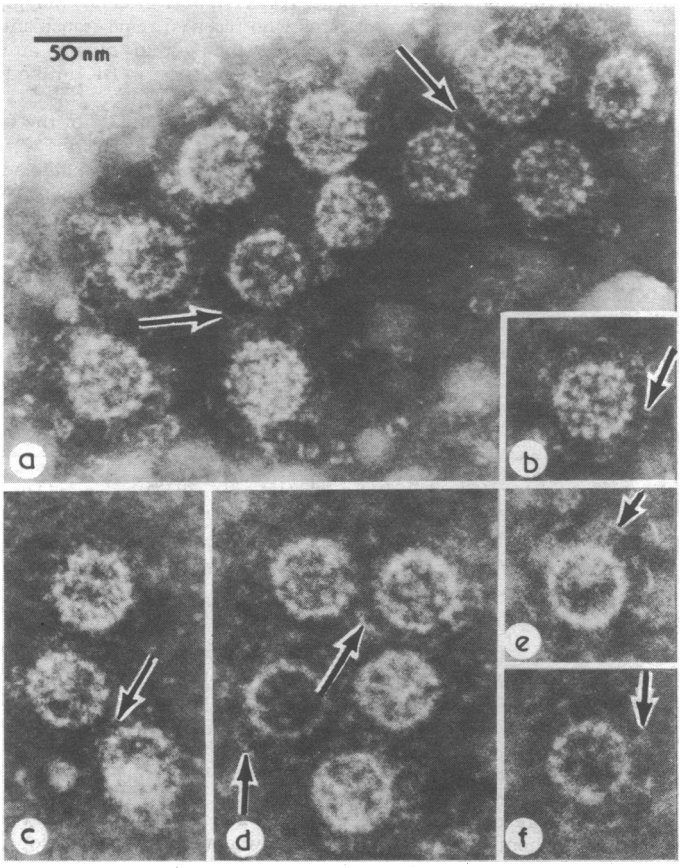
TABLE II—*Total BK-virus-specific IgM (as reciprocal titres*) in renal transplant recipients, patients with malignant disease, and controls*

	Transplant recipients		Patients with malignant disease	Controls
	Before	After		
No of subjects	20	20	57	66
No (%) with BK-virus-specific IgM	2 (10)	7 (35)	6 (10·5)	13 (19·6)
Range of titre	30–50	5–$\geqslant$1120	20–240	10–$\geqslant$330
Median titre	39	480	91	21
Geometrical mean titre	39	223	69	28

*Calculated by summation of fraction titres and multiplication by dilution factor.[52]

The duration of the BK-specific IgM response in patients with malignant disease could not be determined since only a single serum sample was collected; however, a second serum sample collected from two controls whose first sera had contained BK-virus-specific IgM showed that it had persisted in these two people for 33 and 37 months.

The detection of apparent virus-specific IgM in a relatively high proportion of controls raised the possibility that this may have merely represented a 2-mercaptoethanol-sensitive inhibitor with a density similar to that of IgM. The IgM fractions of sera from one renal transplant recipient, one patient with breast cancer, and seven controls who apparently had BK-virus-specific IgM HAI antibody were therefore examined by immune electron microscopy. Typical IgM bonding was evident when these fractions were reacted with BK virus (see figure; A, B, D, E, and F) except in two controls whose BK HAI antibody titre in the IgM fraction was $\leqslant$1/20. This probably reflects



Immune electron microscopy: BK virus complexed with serum fractions and examined after negative staining. Arrows show immunoglobulin molecules. (A and B) IgM fraction from renal transplant recipient. Note conspicuous "loop-like" or "staple-like" IgM molecules (arrowed). (C) IgG fraction from renal transplant recipient; IgG molecules are much smaller (arrowed). (D, E, and F) IgM fraction from control.

the degree of sensitivity of the immune electron microscopy method. IgG-containing fractions from the same renal transplant recipient and one of the healthy controls showed typical IgG aggregation of virus particles (see figure; C). Similarly, no IgM-like bonding was detected when fractionated serum samples known to contain a high titre of BK-virus-specific IgG but no IgM were reacted with BK virus.

To demonstrate that this IgM bonding was BK specific the same fractions from the renal transplant recipient and one of the apparently healthy controls, both of which contained BK-virus-specific IgM by immune electron microscopy, were reacted with another papovavirus, SV40. No bonding occurred when the fraction containing BK-specific IgM from the apparently healthy controls was reacted with SV40, but the IgM-containing fraction which contained a particularly high BK HAI titre ($\geq 1/220$) from the renal transplant recipient showed reaction at a very low level (bonding of one IgM molecule). The IgG-containing fractions from these sera did not aggregate SV40 virus particles.

As a further test of specificity, a control serum sample known to contain a high level of RDE-sensitive, but 2-mercaptoethanol-resistant BK-virus inhibitor in the IgM fractions, was fractionated without pretreatment and reacted with BK virus. No IgM-like bonding was detected.

Discussion

Our studies do not indicate whether the patients who had primary BK-virus infection after transplantation acquired infection with the graft, by transfusion, or by alternative exogenous sources. Our findings do show, however, that BK-virus infections in patients undergoing renal transplantation are associated with persistent virus-specific IgM responses; Jung *et al* also detected BK-virus-specific IgM responses in four renal transplant recipients[16] but did not find it in four healthy controls.[22] We, however, also detected BK-virus-specific IgM in patients with malignant disease and apparently healthy people. So far as we are aware this has not been reported. The specificity of these observations was supported by immune electron microscopy studies, in which typical IgM bonding to BK virus was observed; this looked similar to that observed when foot-and-mouth-disease virus was reacted with guinea-pig IgM or IgG serum fractions containing antibody to this virus.[23] Additional support for specificity was provided by immune electron microscopy studies with the papovavirus SV40. The IgM bonding detected at a low level between serum fractions from one renal transplant recipient with a particularly high level of BK-virus-specific IgM probably confirms a report of minor cross-reactions by immune electron microscopy between SV40 and BK-virus antiserum.[24]

Virus-specific IgM is detected in human serum after primary infection with many viruses, and it usually declines to undetectable levels 60-90 days after onset.[18 25-29] Nevertheless, low levels of virus-specific IgM may be detected up to a year after uncomplicated naturally acquired and vaccine-induced infection by rubella[30 31] and up to two years after infection by Japanese encephalitic virus.[32 33] A virus-specific IgM response may also occur when such latent infections as varicella zoster or herpes simplex are reactivated[34 35]; we detected BK-virus-specific IgM in an immune patient whose antibody titre rose significantly after transplantation. This presumably resulted from reactivation of endogenous virus.

In addition to primary infections and virus reactivation, virus-specific IgM may also be detected in some persistent virus infections—for example, subacute sclerosing panencephalitis,[9 10] cytomegalovirus infections in immunocompromised patients,[15] and congenitally acquired rubella and cytomegalovirus infections.[11-14] So far as we are aware, however, the 13 controls whose serum contained virus-specific IgM were in good health. Three of these had relatively high BK-virus-specific IgM titres. Although we could not assess the duration of BK-virus-specific IgM in most of the controls, it persisted for about three years in the two from whom second samples were obtained. The duration of virus-specific IgM is a direct function of virus dose,[36] and depletion of viral antigen terminates IgM synthesis.[37] Since the half life of IgM is four or five days,[38] persistence of BK-virus-specific IgM for up to three years suggests that BK virus continued to provide an antigenic stimulus. Although the site of virus replication can only be speculative, the detection of BK virus in the urine of renal transplant recipients[16 39 40] may suggest that replication occurs in the renal tract. BK virus, however, has been isolated not only from the urine but also from the brain tumour of a child with Wiscott-Aldrich syndrome.[41] JC virus, another human papovavirus with a widely prevalent HAI antibody in man,[42] and viruses antigenically closely related to SV40[43] may also be associated with persistent infections, having been isolated from the brains of patients with progressive multifocal leucoencephalopathy.[7 44] JC virus has now also been identified in the urine of a renal transplant recipient with no clinical evidence of progressive multifocal leucoencephalopathy.[7]

In this retrospective study there was no obvious clinical association between the serological evidence of BK virus activity and any serious clinical effect on the renal transplant recipient. Elucidation of the clinical significance of BK-virus infection in immunocompromised patients is likely to yield such information only if studies are conducted prospectively correlating clinical and virological data. Such studies must, however, also include investigations to detect evidence of infection by other groups of viruses which may cause problems in immunosuppressed patients—for example, the herpes group of viruses[45-50] and hepatitis B virus.[51]

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Requests for reprints should be sent to JEB.

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Femoral vein thrombosis and total hip replacement*

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Summary

Of 160 patients who underwent total hip replacement, 81 developed venographic evidence of thrombi in the operated leg. In 46 cases (57%) the thrombus originated from the femoral vein, and in 43 of these the exact site of origin was defined by venography. In 34 cases (74%) the thrombus arose from the wall of the femoral vein at the level of the lesser trochanter. This region was studied by intraoperative venography in eight patients undergoing total hip replacement, and in every case severe distortion of the common femoral vein was observed, producing almost total occlusion.

We suggest that intraoperative damage to the femoral vein results from manipulation of the leg, and that this is one reason why the operation is followed by a high incidence of deep vein thrombosis in the upper femoral region.

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Introduction

Total replacement of the hip joint has become increasingly popular recently. Nevertheless, prospective studies, using the ^{125}I-fibrinogen test and ascending venography, have shown that it is associated with a high incidence of thromboembolic complications.[1-5] Furthermore, necropsy studies on patients dying in the postoperative period indicate that pulmonary embolism is the most common cause of death after this operation.[6-8] Many factors contribute to deep vein thrombosis (DVT) in these high-risk patients.[9] The distribution of venous thrombi in 81 patients with venographically evident DVT after total hip replacement suggested that a thrombogenic stimulus existed in the region of the proximal femoral vein in the operated leg. We studied this further by visualising the femoral vein intraoperatively by means of ascending venography.

Patients and methods

One hundred and sixty patients who underwent total hip replacement were studied for postoperative DVT. All gave written, informed