Cytomegalovirus and BK-Virus co-infection of a clinically non-functioning adrenal adenoma: innocent bystanders or new pathogenetic agents?

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We report a case of a 64-year-old woman who underwent left adrenalectomy with removal of a 8,5 cm clinically non-functioning adrenocortical adenoma and a 4-cm myelolipoma. Molecular testing for viral infection demonstrated the presence of cytomegalovirus (CMV) DNA sequences in the adrenal adenoma, but not in the myelolipoma (confirmed by immunohistochemistry). Moreover, the adrenal adenoma was also positive for parvovirus B19, and both adrenal tumor samples were positive for polyomavirus BK (BKV) and adenovirus DNA sequences. This is the first report of co-infection of an adrenocortical adenoma by CMV and BKV. The role of these viruses in adrenal tumorigenesis was postulated.

Key words: cytomegalovirus, BK-virus, adrenal adenoma.

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Clinically silent adrenal masses discovered by imaging studies performed for unrelated reasons (adrenal incidentaloma, AI) are a rather common finding in clinical practice, being encountered in 0.5-2% of abdominal computed tomography scans (Barzon *et al.,* 2003). The pathogenetic mechanisms at the basis of the development of adrenal masses are still largely unknown. Several viruses, including polyomaviruses and herpes viruses, can cause cancer in humans (Nevins, 2001) and some of these viruses have been demonstrated to have tropism for the adrenal gland (Small *et al.,* 1986; Pulakhandam and Dincsoy, 1990). However, the role of viruses in the pathogenesis of adrenal tumours has not been investigated so far in the literature.

We have studied a case of double left AI in a 64-year-old woman. CT-scan showed the a 8,5 cm hypodense adrenal mass with poor enhancement connected with a second 4 cm adrenal mass with density greater than water (Figure 1). The patient was not immunosuppressed and endocrine evaluation of adrenal cortical and medullary function showed normal hormone levels. After a surgical excision, pathological examination diagnosed the larger mass as myelolipoma (ML) and the smaller as adrenal adenoma (AA).

We performed PCR analyses on both ML and AA samples to investigate the presence of sequences of the following viruses: Epstein-Barr Virus, cytomegalovirus (CMV), Herpes simplex virus-1 (HSV-1), HSV-2, polyomavirus BK (BKV), polyomavirus JC, Simian Virus 40, Human Papilloma Virus-16, parvovirus B19, and adenovirus, finding the presence of CMV DNA in the AA specimens but not in the ML ones. The adenoma was also positive for parvovirus B19 DNA, and both tumour samples

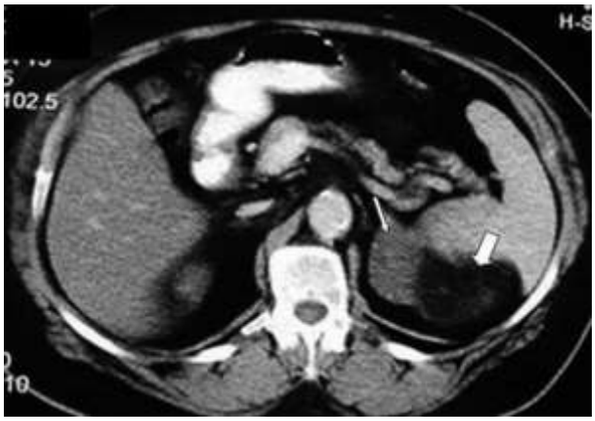

Figure 1. Enhanced abdominal CT scan revealed a left double adrenal mass: a myelolipoma (wide arrow) and an adrenal adenoma (thin arrow).

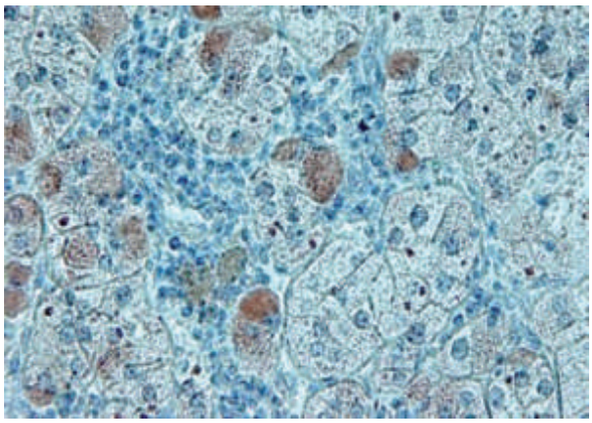

Figure 2. Immunohistochemical analysis showed glomerulosa-type cells of the adenoma positive for CMV, localized in the cytoplasm of 15% of cells with a variable intensity of stain.

were positive for BKV and adenovirus DNA sequences. Immunohistochemical analysis for CMV early antigens showed diffuse positive staining only in the adrenocortical adenoma (Figure 2).

Our study represents the first report of CMV and BKV co-infection of an AA. The findings of CMV and BKV infection in a non-functioning AA, but not in the nearby adrenal ML could permit us to speculate on a possible role of viruses on the promotion of adrenocortical cell proliferation. Indeed, human CMV has been demonstrated to be associated with human malignancies and to transform a variety of mammalian cells in vitro and in vivo (Doniger *et al.,* 1999; Mundle *et al.,* 2001). Moreover, it contains genes involved in cell cycle control and apoptosis inhibition, in analogy to other herpes viruses, namely the oncogenic gamma herpes viruses (Lulac *et al.,* 1999). The presence of BKV infection is also intriguing, since this human polyomavirus has adrenal tropism and has been recently associated with several human cancers (Tognon *et al.,* 2003). An interaction between the two viruses could therefore occur with relevant pro-oncogenic implications. Concerning the other viruses detected in the tumour samples, the presence of adenovirus and parvovirus B19 DNA sequences, which were found at lower levels, could be related to infection of vascular cells or circulating blood cells. Although unlikely, a role for these viruses in adrenal tumorigenesis can not be ruled out, especially for adenoviruses.

In conclusion, we believe that this finding of CMV and BKV co-infection of an adrenal adenoma could suggest to research for these viruses in other adrenal tumours, to better clarify their role in pathogenesis of human cancers.

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