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LETTER TO THE EDITOR

Circulating cell-free DNA for response evaluation of intravascular lymphoma

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Dear Editor,

Circulating cell-free tumor DNA (ctDNA) is detectable in the plasma of cancer patients. It has been shown that copy number aberrations (CNAs) can be detected by shallow whole-genome sequencing (sWGS) of circulating cell-free DNA (cfDNA) from patients with Hodgkin lymphoma [1]. Changes in the levels of cfDNA have been associated with tumor burden [2]. Liquid biopsies in the form of blood draws to analyze cfDNA may potentially provide diagnostic, prognostic, and therapeutic value.

Intravascular large B cell lymphoma (IVLBCL) is characterized by the predominant growth of large cells within the lumen of small blood vessels [3]. It is rapidly progressive, but prone to diagnostic delay because of the nonspecific nature of presenting symptoms [4]. Sites of lymphoma may not be apparent on imaging studies. Since lymphoma cells are difficult to detect at diagnosis, it is not clear how response evaluation should be performed. Its location within the bloodstream and its high proliferative index [3] make liquid biopsy an attractive option to monitor therapy efficacy.

We treated a 61-year-old patient with IVLBCL, diagnosed on kidney biopsy and presenting with high fever, with six cycles R-DA-EPOCH and two cycles of high-dose methotrexate. Genome-wide copy number profiles and pathology are shown in Figs. 1 and 2. Liquid biopsy after three cycles of R-DA-EPOCH and after completion of therapy could not demonstrate ctDNA. This was confirmed by repeated kidney biopsy (Fig. 2d). One year after therapy, the patient is still in complete remission.

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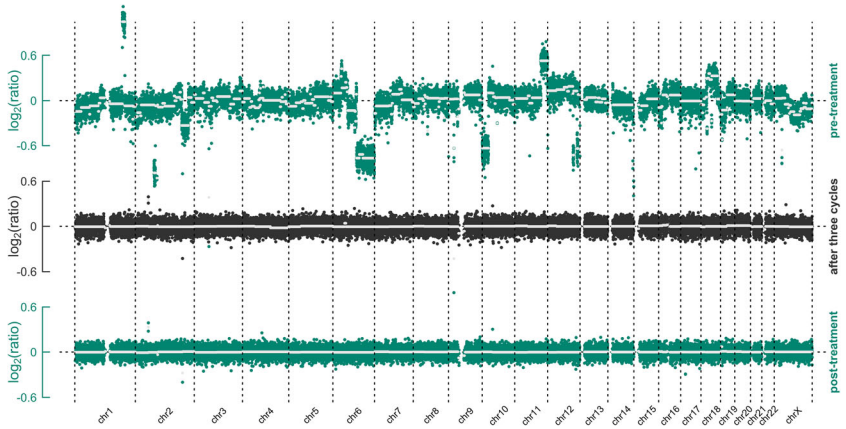

Fig. 1 Genome-wide copy number profiles obtained from shallow whole-genome sequencing of cell-free DNA (cfDNA). The methodology used here is essentially the same as for non-invasive prenatal testing (NIPT) for fetal aneuploidies [5]. Log_2-transformed ratios between the observed and expected (for the normal diploid state) number of reads per window (bin) of 100 kb are plotted across all chromosomes and are represented as a dot. A positive log_2 ratio indicates a chromosomal gain (blue), while a negative log_2 ratio indicates a loss (red). Analysis of cfDNA at diagnosis showed many copy number aberrations, gains as well as losses (CNAs) (top panel). After three cycles R-DA-EPOCH no CNAs could be detected (middle panel). Analysis of cfDNA after treatment shows again a flat profile (bottom panel)

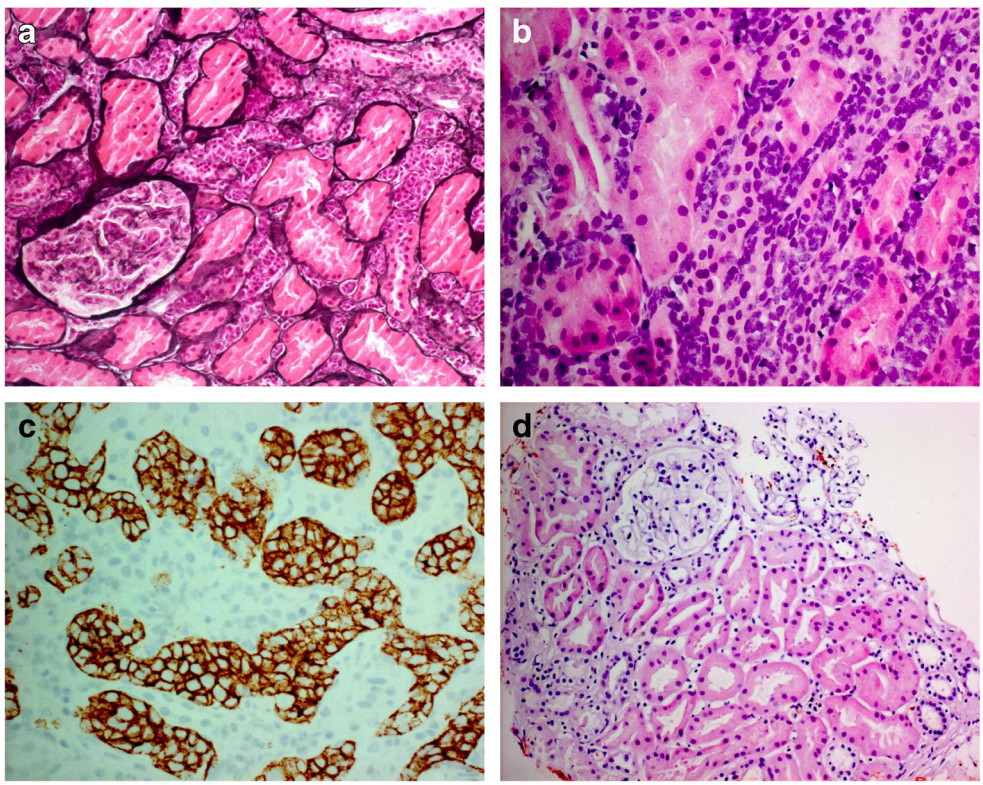

Fig. 2 **a** Renal biopsy, Jones stain, × 20: Glomeruli and tubules show no abnormalities. The interstitial capillaries are filled with atypical lymphoid cells. **b** Renal biopsy, H&E stain, × 40: The atypical lymphoid cells are medium-sized with irregular, slightly hyperchromatic nuclei. **c** Renal biopsy, immunohistochemical stain for CD20, × 40: the atypical lymphoid cells show strong membranous staining for CD20. Most cells display weak membranous positivity for CD5 (not shown). They are negative for myeloperoxidase, CD3, CD10, CD56, TDT, SOX11, and cycline D1. D: Renal biopsy, H&E, × 40: after treatment, no residual atypical lymphoid cells are morphologically recognizable

Compliance with ethical standards

Ethics All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed consent Informed consent was obtained from all patients for being included in the study.

Conflict of interest The authors declare that they have no conflicts of interest.

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