Supplementary methods

H&E staining. Tissue sections were deparaffinized in xylene substitute (cat. no. ZLI-9315; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) for 20 min twice, and rehydrated using graded ethanol (100, 95, 80 and 70%) and distilled water. Sections were then stained with hematoxylin (cat. no. G1004; Wuhan Servicebio Technology Co., Ltd.) for 8 min at room temperature (~25˚C), rinsed in running tap water for 20 min, differentiated in differentiation solution (cat. no. G1039; Wuhan Servicebio Technology Co., Ltd.) for 2 sec, rinsed in tap water for 10 min, blued in bluing solution (cat. no. G1040; Wuhan Servicebio Technology Co., Ltd.) for 2 sec and rinsed in tap water for 10 min. After dehydration using graded ethanol, the sections were stained with eosin (cat. no. G1001; Wuhan Servicebio Technology Co., Ltd.) for 2 min at room temperature, cleared in xylene and mounted with mounting medium (cat. no. ZLI-9516; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd).

Immunohistochemistry. After deparaffinization and rehydration as aforementioned, antigen retrieval was performed by heating the sections in citrate buffer (pH 6.0; cat. no. G1202; Wuhan Servicebio Technology Co., Ltd.) using a pressure cooker for 3 min after boiling, followed by natural cooling to room temperature. Endogenous peroxidase activity was blocked with peroxidase blocking reagent (reagent 1; cat. no. PV-9000; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) for 10 min. Non-specific binding was blocked with normal goat serum (cat. no. ZLI-9056; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) for 40 min to 1 h at room temperature. Sections were then incubated with primary antibodies overnight at 4˚C. After washing, sections were incubated with an enhancing reagent (reagent 2; cat. no. PV-9000; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) for 20 min, followed by incubation with appropriate HRP-conjugated secondary antibodies (reagent 3; cat. no. PV-9000; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) for 40 min at room temperature. The signal was visualized using DAB substrate (cat. no. ZLI-9018; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), and nuclei were counterstained with hematoxylin (cat. no. G1004; Wuhan Servicebio Technology Co., Ltd.) for 5 min. The following primary antibodies were used: Anti-EBV LMP-1 (mouse monoclonal; clone CS 1-4; dilution 1:100; cat. no. ab78113; Abcam), anti-p63 (mouse monoclonal; clone 4A4; dilution 1:100; cat. no. ab735; Abcam) and anti-CK5/6 (mouse monoclonal; clone D5/16B4; dilution 1:50; cat. no. ab17133; Abcam). HRP-conjugated goat anti-rabbit/mouse IgG complex (reagent 3; cat. no. PV-9000; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) was then applied and incubated for 40 min at room temperature according to the manufacturer's instructions.

EBER in situ hybridization. Tissue sections (4-6 μm) on poly-L-lysine-coated slides were baked at 56-60˚C for 2-16 h, deparaffinized in xylene twice (10 min each), immersed in absolute ethanol for 2 min and air-dried for 5 min. After digestion with pepsin working solution (100 μl/section; diluted 1:100 in 0.1 N HCl) at 37˚C for 20 min, sections were dehydrated in graded alcohols and air-dried (1 min each, 3 changes). EBER probe (5 μl/section) was applied, covered with a coverslip and hybridized at 37˚C for 2 h. Coverslips were removed in PBS, and sections were washed three times for 2 min each in PBS. For detection, HRP-conjugated anti-digoxigenin antibody was applied (37˚C for 20 min), followed by PBS washes (three times for 2 min each). Signal was visualized with DAB working solution (5-15 min, monitored microscopically). Nuclei were counterstained with hematoxylin (20 sec), rinsed, differentiated in 1% HCl (2-5 sec), blued in lithium carbonate (30 sec-1 min), and washed thoroughly. Finally, sections were dehydrated in graded ethanol, cleared in xylene and mounted with neutral balsam for microscopic examination.