Abstract
Chordoma is a rare slow-growing tumor thought to arise from remnants of the notochord, since brachyury, a notochordal transcriptional factor, is expressed in chordoma cells. Chordoma occurs in the skull base or the spine and destroys these bones and expands. In the skull-base chordoma deriving from the clivus, abnormal eye movement and swallowing disorder are the major symptoms caused by bone destruction and compression of surrounding structures such as cavernous sinus and the nasopharynx. Complete resection of chordoma is difficult due to the presence of the brainstem, cranial nerves and arteries around the clivus. The effect of conventional radiotherapy and chemotherapy are limited; thus, a new therapeutic approach is required. In this study, we focused on the mechanism of bone destruction by chordoma. The current paradigm is that osteolytic tumors produce various cytokines thereby inducing osteoclast formation directly or indirectly. However, we found the possibility that chordoma cells themselves secrete acid and proteases and destroy bone. The micro-CT analysis indicated that the patient's skull base destructed by chordoma exhibited highly porous bone tissue with low mineral density. Immunohistochemical analysis showed that there were brachyury-positive chordoma cells in the porous structures of the clivus, and these cells produced proteases such as cathepsin K and MMP-13. Human chordoma JHC7 cells contained several large acidic vacuoles as visualized by acidic pH-sensitive LysoSensor probe. Furthermore, multinucleation of JHC7 cells through cell fusion was observed in live cell imaging. These data support a view that chordoma cells located at the bone surface form osteoclast-like multinucleated giant cells to destroy bone tissue.