Prominence of nestin-expressing Schwann-like cells in the bone marrow of myelodysplastic syndromes with severe fibrosis

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論文の内容の要旨
Abstract of thesis

（目的　Purpose）

Nestin-expressing stromal cells (NESCs) and Schwann cells in the bone marrow (BM) play crucial roles as a niche for normal hematopoietic stem cells in mice. Both of these types of cells were reportedly decreased in myeloproliferative neoplasms (MPN) patients and also in a mouse model. Conversely, an increase in NESCs was reported in acute myeloid leukemia. Accordingly, it is of interest whether and how these BM stromal cells are structured in myelodysplastic syndromes (MDS). In this study, the author focused on NESCs and glial fibrillary acidic protein (GFAP)-expressing stromal cells in the BM of MDS patients.

（対象と方法　Materials and Methods）

Forty-five patients with MDS, and 16 patients with MPN divided into two groups as MPN-associated MF (12 cases) and chronic myelogenous leukemia (CML) (4 cases) were enrolled in the study. Samples from 17 patients with non-Hodgkin lymphoma (NHL) without BM involvement were analyzed as the control. The author used archived formalin-fixed paraffin-embedded (FFPE) BM biopsy samples from these patients for silver staining and immunostaining, and mononuclear frozen cells BM aspirate samples for genetic analysis. Immunostaining were performed with antibodies against nestin, CD34, *α-smooth muscle actin (α-SMA)*, GFAP, neurofilament heavy chain

(NFH), and others.

（結果　Results）
The author identified 19 (42.2%) MDS with fibrosis (MDS-F) cases, 7 (15.5%) had fibrosis grade 3 (MF3) and 12 (26.7%) had MF2, and 26 (57.8%) remaining patients identified as MDS without fibrosis (MDS w/o F), 11 (24.5%) were MF1, and 15 (33.3%), as MF0. The 12 MPN-associated MF cases were evaluated as MF2 or MF3. The author found a marked increase of NESCs in MDS-F patients at a high frequency (9/19; 47.4%), but not in MDS w/o F (0/26; 0%) and MPN (0/12; 0%) patients, including both MPN-associated MF and CML. In 8 of the 9 MDS-F cases (88.9%) with the NESC increase, a majority of NESCs also expressed GFAP, with an additional increase in GFAP single-positive cells. Furthermore, in 7 of them, the author found a prominent structure characterized by NFH staining surrounded by NESCs with GFAP expression or GFAP single-positive cells.

（考察　Discussion）
These findings suggest that increase of NESCs in BM of MDS-F patients may have an important role in promotion of BM myelofibrosis. According to immunostaining results, NESCs expressing the GFAP may represent the rejuvenated Schwann cells that start to proliferate with some stimulation in MDS-F, but not in MPN-associated MF. Therefore, nestin may have a potential marker to distinguish MDS-F and MPN-associated MF. In addition, it is reasonable to hypothesize that the abnormally enhanced Schwann cell proliferation induces axonal extension. Consequently, the increase in nestin-expressing Schwann-like cells in the BM is likely to have a significance in the pathophysiology of myelofibrosis in patients with MDS.

審査の結果の要旨
Abstract of assessment result

（批評　General Comments）
The author has identified a unique subgroup of MDS-F characterized by the abnormal proliferation of a structure comprising terminal nerve axons and the surrounding Schwann-like cells, typically accompanying severe fibrosis and hypercellular BM. This structure could have a relevance to the pathophysiology of MDS-F and might be useful marker for clinical diagnosis.

（最終試験の結果　Assessment）
The final examination committee conducted a meeting as a final examination on Jan 11, 2019. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

（結論　Conclusion）
The final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.