News Release

Title

Targetable driver mutations in multicentric reticulohistiocytosis

Key Points

- **We identified FGFR1 tyrosine kinase fusion (KIF5B-FGFR1) and MAP2K1 (MEK1) gain-of-function mutation in patients with multicentric reticulohistiocytosis (MRH) which has been suspected to be an autoimmune or inflammatory disease. Our results suggest that MRH is not an autoimmune or an inflammatory disease but a neoplastic one.**
- **We administered a chemotherapy to a patient with the MAP2K1 mutation, and we observed improvement of both subjective and objective symptoms.**
- **Further studies are warranted to contribute to the development of optimal therapeutic approaches including chemotherapy and target therapy for MRH**

Summary 1

Prof. Yoshihiro Nishida in Department of Rehabilitation, Nagoya University Hospital, Dr. Yusuke Okuno in Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Dr. Norihiro Murakami in Department of Pediatrics, Nagoya University Graduate School of Medicine, Dr. Tomohisa Sakai in Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine and their colleagues performed a molecular profiling of multicentric reticulohistiocytosis. Multicentric reticulohistiocytosis (MRH) is an extremely rare histiocytic disease characterized by papulonodular skin lesions and multiple destructive arthritic lesions resembling those of rheumatoid arthritis. MRH has been suspected to be an autoimmune or inflammatory disease; however, the molecular pathogenesis of MRH is poorly understood and current treatments using anti-inflammatory agents are inadequate. Here, we show that histiocytes in MRH patients carry a KIF5B-FGFR1 tyrosine kinase fusion or a MAP2K1 (MEK1) gain-of-function mutation, suggesting the neoplastic nature of this disease and the possibility for molecular targeted therapies. One patient with MRH that was refractory to conventional therapies using anti-inflammatory agents showed a clinically meaningful response to a chemotherapeutic regimen used for Langerhans cell histiocytosis, although we stopped the treatment because of adverse effects. Our results might contribute to the development of treatment strategies, including molecular targeted therapies, for MRH.

Summary 2

We identified FGFR1 tyrosine kinase fusion (KIF5B-FGFR1) and MAP2K1 (MEK1) gain-of-function mutation in patients with multicentric reticulohistiocytosis (MRH) which has

been suspected to be an autoimmune or inflammatory disease. Our results suggest that MRH is not an autoimmune or an inflammatory disease but a neoplastic one.

Research Background

Multicentric reticulohistiocytosis (MRH) is a very rare systemic disease, characterized by multiple destructive arthritic and papulonodular skin lesions that can also affect other organs including the lungs and heart. Given its similar clinical manifestations with those of rheumatoid arthritis (RA), MRH has been suspected to be an autoimmune or inflammatory disease, and treatments similar to that of RA including administration of corticosteroids, methotrexate, bisphosphonates, and several biological anti-inflammatory agents (etanercept, adalimumab, and infliximab) have been tried. Although spontaneous remission is occasionally observed during the initial 10 years after diagnosis, the functional prognosis is usually poor; joint replacement surgery has often been required because of the progression of destructive arthritis, and current treatment is inadequate especially in severe cases.

Research Results

We performed whole exome sequencing and RNA sequencing in two patients with MRH, and identified a FGFR1 tyrosine kinase fusion (KIF5B-FGFR1) in UPN1 (**Figure 1**) and a MAP2K1 (MEK1) gain-of-function mutation in UPN2, suggesting the neoplastic nature of this disease and the possibility for molecular targeted therapies. One patient with MRH that was refractory to conventional therapies using anti-inflammatory agents showed a clinically meaningful response to a chemotherapeutic regimen (**Figure 2**).

Research Summary and Future Perspective

We identified driver mutations in two patients with MRH. Our results indicate that MRH should be considered a neoplastic disease and suggest promising effects of chemotherapy for its treatment. Further studies are warranted to contribute to the development of optimal therapeutic approaches for MRH, possibly including molecular targeted therapies.

Publication

Murakami N, Sakai T, Arai E, Muramatsu H, Ichikawa D, Asai S, Shimoyama Y, Ishiguro N, Takahashi Y, Okuno Y, Nishida Y, [1]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan. [2]Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan. [3]Department of Pathology and Laboratory Medicine, Nagoya University Hospital, Nagoya, Japan. [4]Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan. [5]Department of Rehabilitation, Nagoya University Hospital, Nagoya, Japan. Targetable driver mutations in multicentric reticulohistiocytosis, Haematologica, 2019 Jun 6.
DOI: 10.3324/haematol.2019.218735

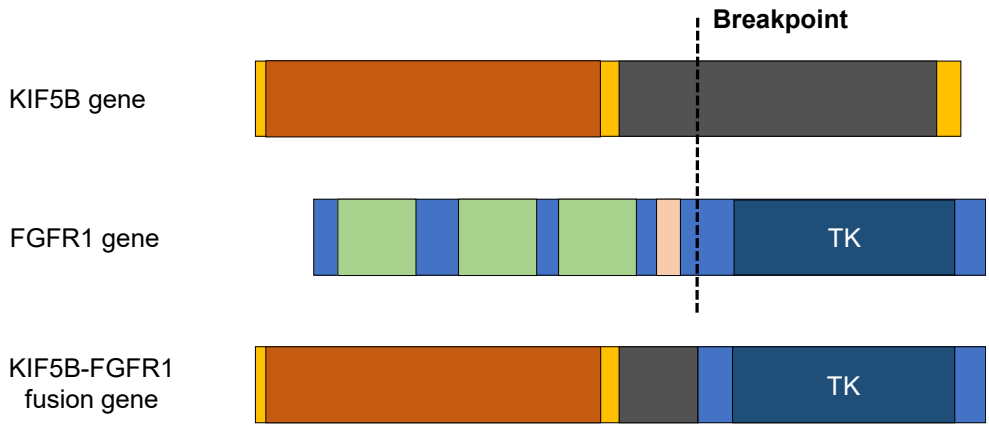

Figure 1. FGFR1 tyrosine kinase fusion gene identified in MRH.
The back part of FGFR1 tyrosine kinase and front part of KIF5B are fused. TK, tyrosine kinase;

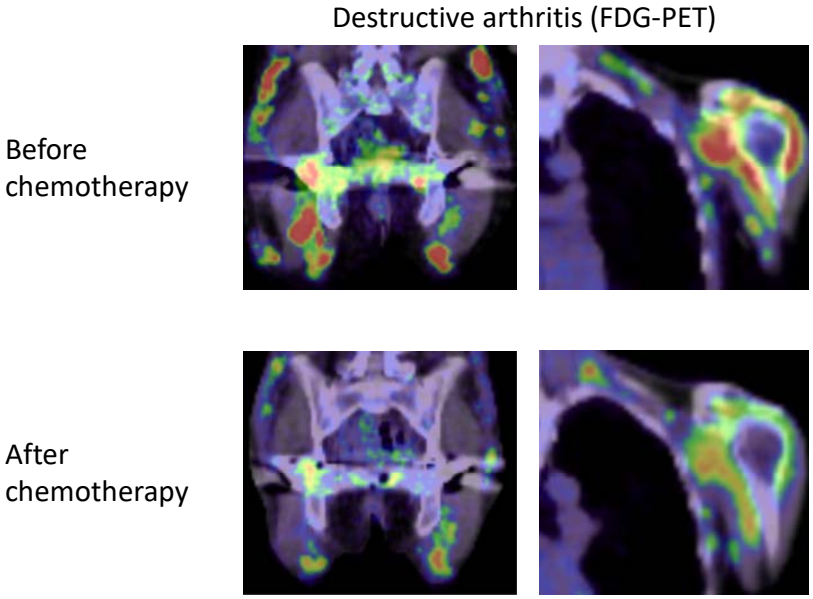

Figure 2. Subjective and objective symptoms before and after treatment
After starting the chemotherapy, the periarticular masses gradually decreased in size and became soft, and metabolic activity of tumorous and inflammatory cells were decreased in FDG-PET.

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