



ALK-positive histiocytosis with disseminated disease responded to alectinib: a case report

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Abstract: ALK-positive histiocytosis is a rare malignancy which was first described in 2008 and recognized as a systemic histiocytic disorder that can affect multiple organs. Less than 20 cases were reported to date, and much fewer cases were presented as disseminated disease, especially with lung and central nervous system (CNS) involvement. The clinical presentation, cytologic and histologic features were diverse in prior reported cases. Diagnosis relied on clinical, pathological findings and might be determined by molecular identification of anaplastic lymphoma kinase (ALK) gene translocation. Exclusion of other tumors such as Erdheim-Chester disease, Langerhans cell histiocytosis (LCH) and histiocytic sarcoma are required. Because of their rarity and diverse features, no standard treatment was applied so far. Here we reported a 51-year-old Asian female patient documented as ALK-positive histiocytosis with lung, intracranial and lymph nodes involvement. Surgery for left frontal tumor resection was performed. Of note was the presence of foam-like histiocytes, epithelioid cells and Touton-like histiocytes scattered in the lesion, emperipolesis also could be observed. Histiocytes were positive immunostaining for CD68/PGM-1, CD163 and ALK1 in cytoplasmic pattern. Fluorescence in situ hybridization (FISH) analysis confirmed ALK gene translocation and next generation sequencing (NGS) revealed KIF5B-ALK fusion. The patient received treatment of second-generation ALK inhibitor-alectinib after diagnosed and showed durable remission. Therefore, our case highlights a new treatment option for this rare entity.

Keywords: Anaplastic lymphoma kinase (ALK); histiocytosis; target therapy; case report

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Introduction

Histiocytosis were a group of proliferative disorders characterized by accumulation of cells derived from mononuclear phagocytes (macrophages and dendritic cells) or histiocytes, usually divided into Langerhans cell histiocytosis (LCH) and non-Langerhans cell histiocytosis (non-LCH) (1). They are rare, difficult to diagnose, and can affect single or multiple organ systems. Anaplastic lymphoma kinase (ALK)-positive histiocytosis, characterized by proliferation of morphologically distinctive histiocytes with a unique expression of ALK,

was first described in 2008 (2). Adult patients had localized lesions in original reports, while pediatric cases were more likely to have a disseminated disease with primarily liver, spleen, or bone marrow affected (3). Because of the rarity of the disease, treatments are personalized. Here, we reported the first case of ALK-positive histiocytosis in an adult patient with systemic disease with lung, central nervous system (CNS) and lymph nodes involvement, and responded to the second-generation ALK inhibitor-alectinib. We present the following case in accordance with the CARE reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-2117>).

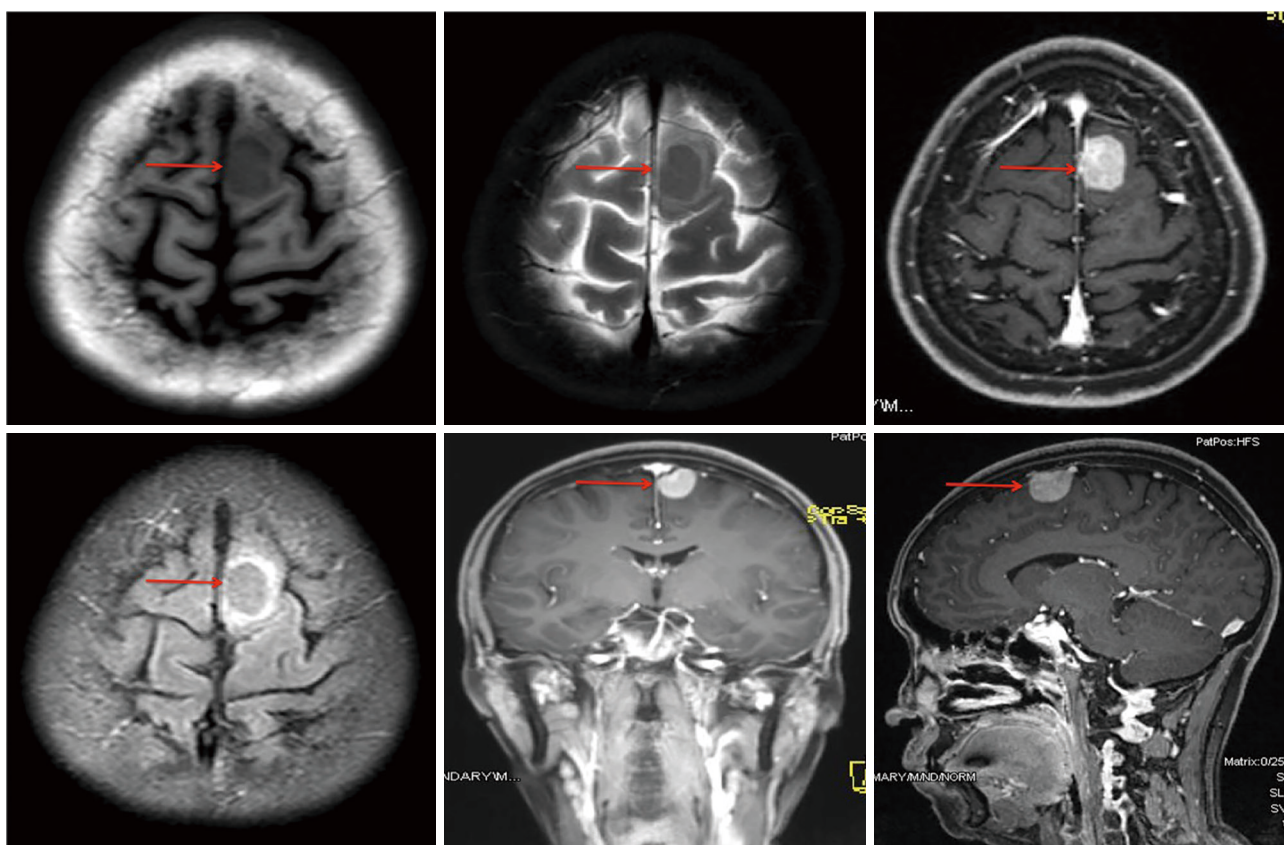


Figure 1 Magnetic resonance imaging of the head before left frontal tumor resection, a mass (red arrows) with a diameter of 1.3 cm \times 1.7 cm \times 1.5 cm was observed in the left frontal lobe (April 13, 2020).

Case presentation

A 51-year-old Asian woman was referred to the hospital in April 2020 for the disseminated nodules with a maximum diameter of 1 cm observed on chest computed tomography (CT). The medical examination reports of the patient revealed that the lung nodules were first found in 2016 in a regular physical check-up, and the patient had received no medical intervention. She received CT reexamination annually with no changes in lung nodules. However, unfortunately, a CT scanning found growth of the nodules this year. The patient is a nonsmoker and had no family history of genetic disease. She had no accompanying symptoms. After being admitted to the hospital, she underwent a 18 fluoro-2-deoxy-d-glucose (FDG) positron emission tomography-CT (PET-CT) scan showing abnormally increased radiopharmaceutical uptake at small disseminated nodules in the lung and a 1.7 cm \times 1.4 cm mass in the left frontal lobe, accompanied

by several lymph nodes involvement. Brain contrast-enhanced magnetic resonance imaging (MRI) showed an oval-shaped mass (about 1.3 cm \times 1.7 cm \times 1.5 cm) next to the falx cerebri in left frontal lobe, manifested as equal T1 and equal T2 signal shadow, and can be markedly enhanced (*Figure 1*).

Considering a malignant tumor, the patient underwent surgery for left frontal tumor resection. Microscopic examination of pathological section showed foam-like histiocytes, epithelioid cells, and a few Touton-like histiocytes were scattered distributed, with small lymphocytes, plasma cells, and few eosinophils in backgrounds (*Figure 2A,2B*). Emperipolesis can be observed. A panel of immunostains was performed, and the histiocytes were positive for CD68/PGM-1 (*Figure 2C*), CD163 and CD23, weakly positive for S-100 and were negative for CD21, CD35, CD1a, Langerin, PCK, EMA, GFAP, TTF-1, PR, STTR2. Uncertain immunoreactive for CD4. No deficiency in INI-1. An ALK1 immunostain

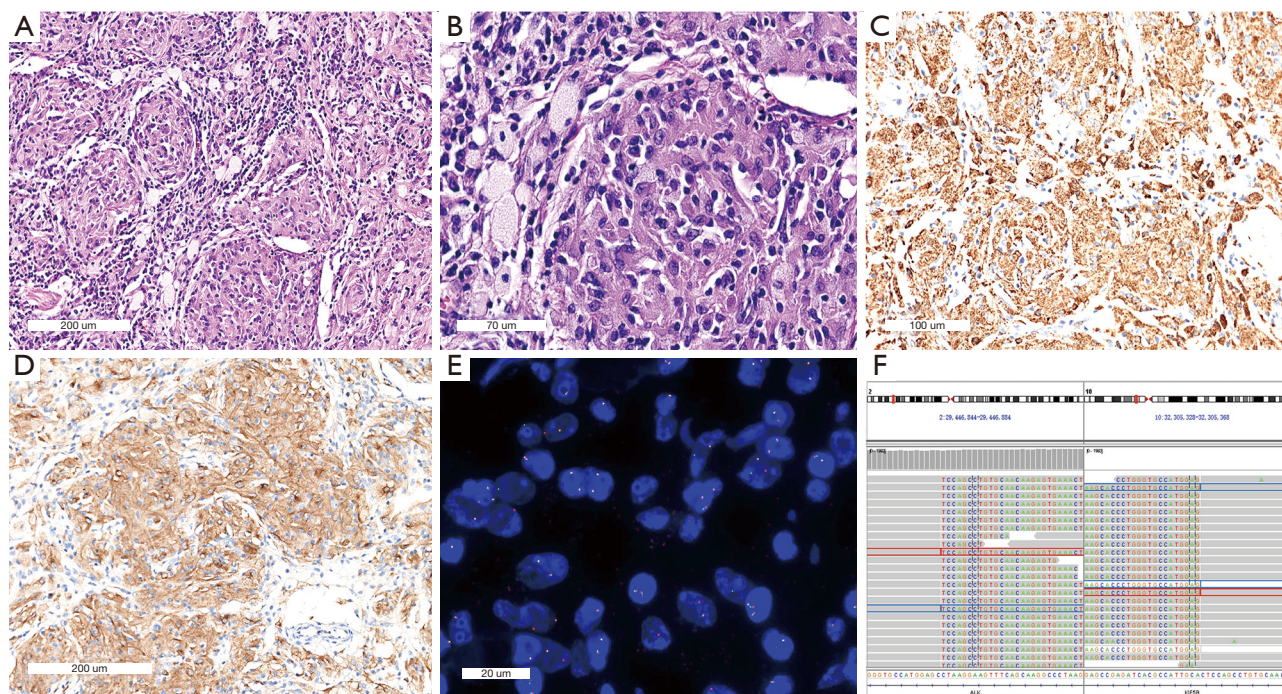


Figure 2 Histopathological and immunohistological findings of ALK-positive histiocytosis. (A) Hematoxylin and eosin staining showed epithelioid cell granuloma formation and infiltrated with foam-like cells (medium magnification). (B) Hematoxylin and eosin staining showed scattered epithelioid cells and foam-like histiocytes (high magnification). (C) The histiocytes showed positive immunostaining for CD68/PGM-1. (D) Atypical cells were positive with the ALK1 IHC stain. (E) Fluorescence *in situ* hybridization using ALK break-apart probe demonstrated ALK rearrangement. (F) Sequencing results confirmed the ALK and KIF5B gene fusion. ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry.

showed cytoplasmic positive (*Figure 2D*). And the index of ki-67 was 1–2%. ALK rearrangement was detected of a formalin-fixed paraffin-embedded tissue section by fluorescence in situ hybridization (FISH) (*Figure 2E*). A next-generation sequencing-based assay was performed, and a KIF5B-ALK fusion was detected (*Figure 2F*). According to the morphology, immunophenotyping, and molecular findings, this case confirmed a diagnosis of ALK-positive histiocytosis.

After surgery, the patient received radiographic reexamination on June 4, 2020. Contrast-enhanced MRI of the head showed slightly swelling of brain tissue in the left frontal lobe operation region, with thickening and enhanced meninges in surrounding areas (*Figure 3*). Chest contrast-enhanced CT showed diffused nodules in bilateral lung and enlarged lymph nodes in bilateral supraclavicular, mediastinal, bilateral hilar, peritoneal, retroperitoneal and bilateral para-iliac vessel area (*Figure 4A*).

After acquired informed consent from the patient, we offered a therapeutic suggestion on target therapy of alectinib began on June 5, 2020. After 3 months, a follow-up computed tomography scan revealed a stable disease (*Figure 4B*). Then, 7 months after receiving alectinib, the radiological assessment showed partial regression in lung and lymph node lesions (*Figure 4C*). At the latest follow-up, 10 months after receiving alectinib, there was still no evidence of progression (*Figure 4D*), and the patient remained in good tolerance.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

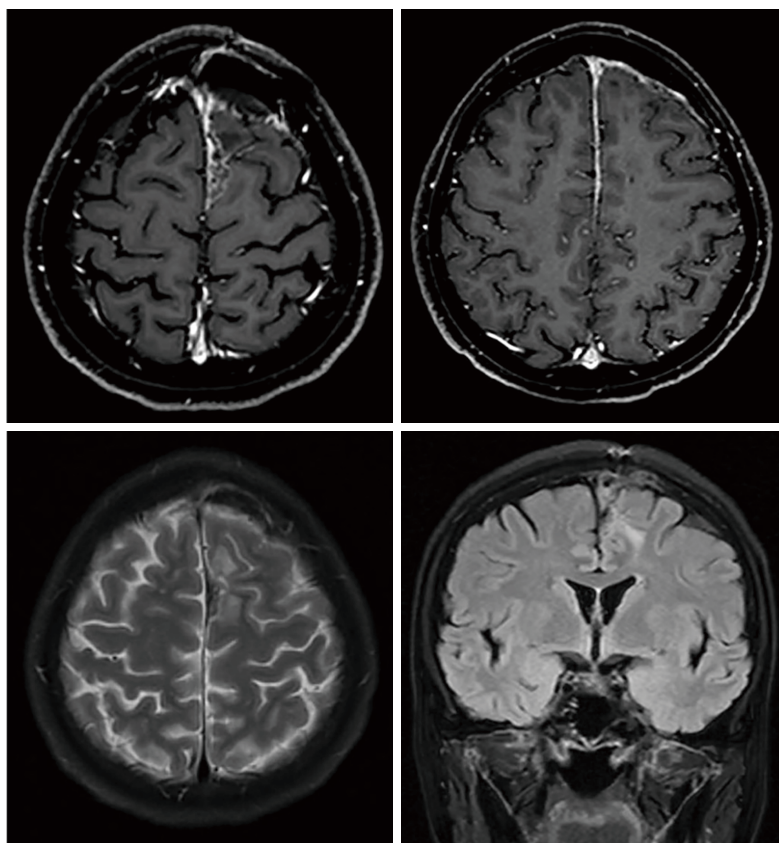


Figure 3 Magnetic resonance imaging of the head. After intracranial tumor resection but before alectinib treatment, MRI showed slightly swelling of brain tissue in the left frontal lobe operation region, with thickening and enhanced meninges in surrounding areas (June 4, 2020).

Discussion

To the best of our knowledge, this is the first case report to discuss the successful management of ALK-positive histiocytosis in a middle-aged person with a systemic disease, including lung, CNS, and lymph nodes involvement, with alectinib.

A histiocytosis is a heterogeneous group of localized or disseminated diseases. Based on previous reports of case series, patients with the systematic disease were neonate or young children, typically manifested with anemia, thrombocytopenia, and hepatosplenomegaly, and affecting liver, spleen, or bone marrow (2). However, with newly reported cases, the clinicopathological spectrum of ALK-positive histiocytosis is wider, including adults presented as localized disease. There were less than 20 cases reported so far. Among them, half patients were younger than 16 years old. Besides, there were more cases presented as localized disease and a preference in Caucasian or Asian (4). Differential diagnosis with other types of histiocytosis,

including LCH, Erdheim-Chester disease, histiocytic sarcoma, etc., remains challenging, relying mainly on clinical, pathological findings and molecular identification of ALK translocation (5). Current treatment strategies considering the proliferative histiocytic diseases remain difficult, including surgical resection in localized disease, chemotherapy or ALK-inhibitors in systemic cases. No standard treatment is recommended because of the low incidence of ALK-positive histiocytosis, and there are limited data on the role of different therapeutics.

Since the first described ALK fusion in anaplastic large cell lymphoma (ALCL), the number of neoplasms recognized to show ALK gene translocation has increased, including lung cancer, inflammatory myofibroblastic tumor, colorectal carcinoma, etc. (6). ALK gene can be fused with different partner genes. Unlike EML4, commonly observed in non-small cell lung cancer (NSCLC), KIF5B has emerged as the most frequent partner gene in ALK-positive histiocytosis, while TPM3 or COLIA2 have also

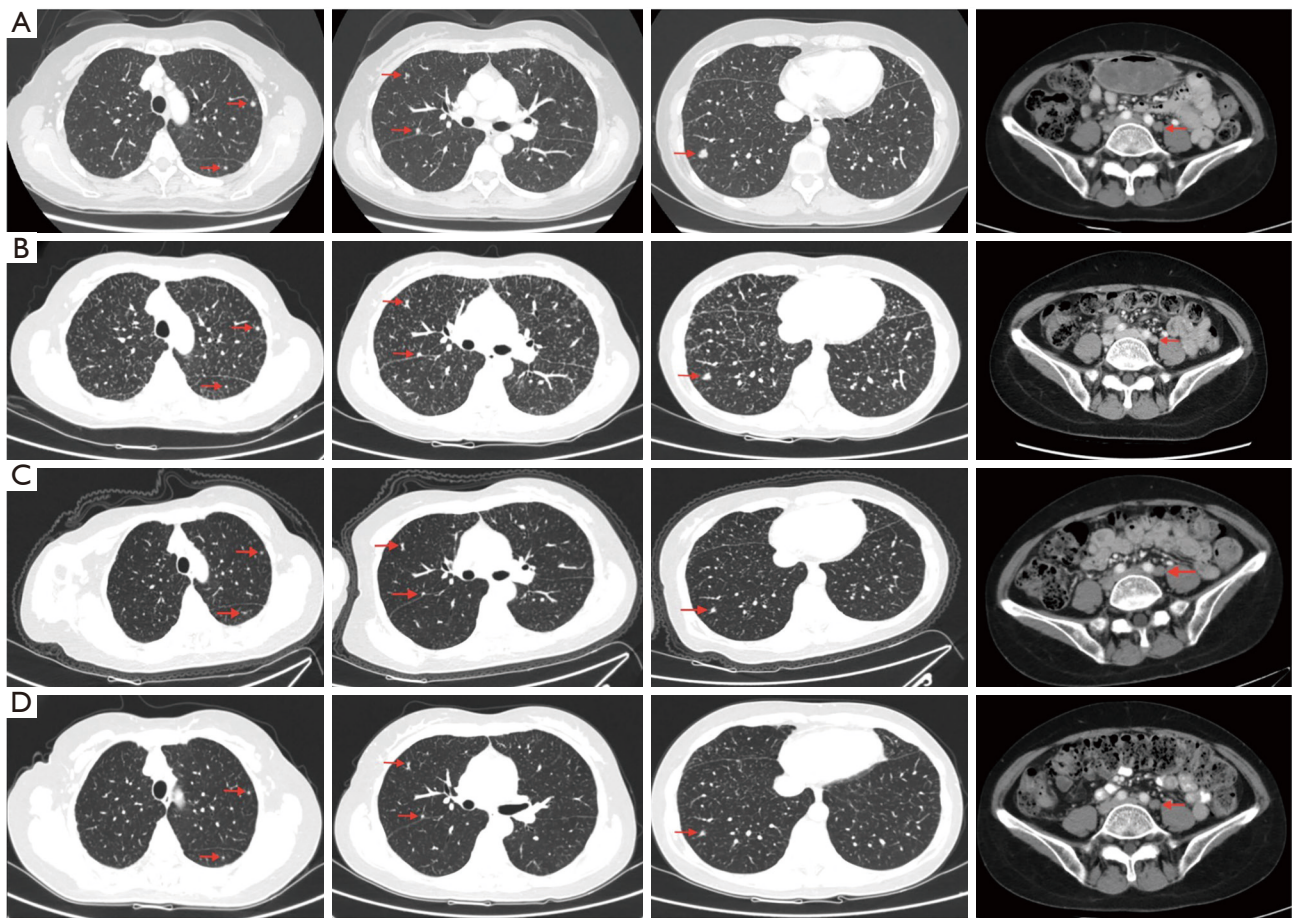


Figure 4 Computed tomography scan of chest and abdomen during treatment. Red arrows highlight the lung lesions and iliac lymph node lesions. (A) Before alectinib treatment, diffused nodules were seen in the bilateral lung, enlarged lymph nodes were observed in the parailiac vessel area (June 4, 2020). (B) After 3 months of alectinib treatment, lung lesions and enlarged iliac lymph nodes lesions remains stable disease (September 28, 2020). (C) After 7 months of alectinib treatment, both lung and iliac lymph nodes lesions were shrunk (January 4, 2021). (D) After 10 months of alectinib treatment, sustained tumor remission was observed (March 30, 2021).

been documented (3). Next generation sequencing plays a vital role in the identification of a specific partner gene. The recognition of ALK rearrangement played an essential role in therapeutic implication. However, the correlation of gene fusion type with disease location or dissemination hasn't been found yet and the impact of fusion partners on the sensitivity to therapies remains under investigation (7). There was limited attempt regarding clinical trials on the clinical efficacy of ALK-inhibitors in ALK-positive tumors, other than lung cancer. Current evidence strongly favors a promising therapeutic effect of ALK tyrosine kinase inhibitors (TKIs) in rare ALK-rearranged tumors. So far, 2 cases, including an ALK-positive histiocytosis with unresectable cavernous sinus lesion and a widespread “non-

langerhans cell histiocytosis” have been reported responding to crizotinib (3,6).

Alectinib is an orally and highly selective ALK inhibitor which has been approved for the first-line treatment of ALK-positive NSCLC based on ALEX trial (8). The progression-free survival (PFS) was significantly improved with alectinib versus crizotinib (34.8 *vs.* 10.9 months), and the safety profile of alectinib compared favorably with that of crizotinib. The common adverse effects of alectinib are constipation, edema, myalgia, etc., and the overwhelming majority of patients are well-tolerated. Besides, according to CNS efficacy results from ALEX study (9), CNS ORR was 85.7% in alectinib group versus 71.4% in crizotinib group in patients who received prior radiotherapy and

78.6% versus 40.0% in those patients had not. Time to CNS progression was significantly longer with alectinib than crizotinib irrespective of baseline CNS metastases. In general, the second-generation ALK-TKI has a potent efficacy in CNS lesion. In the present case, the patient was recognized as KIF5B-ALK translocation and clinically characterized as lung and CNS infiltration. Thus, alectinib was considered as the treatment of choice and remained durable effective, but long-term survival follow-up is needed.

Conclusions

In summary, ALK-positive histiocytosis was considered a new and malignant entity in proliferative disorders. The limited data revealed the disease can respond to ALK inhibitors; our case highlights a new treatment option for this rare entity. However, further research needs to be conducted, and cross-tumor studies are essential.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-2117>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-2117>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written

consent is available for review by the editorial office of this journal.

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