

Large B-cell Lymphoma with IRF4 rearrangement: a pitfall in the pathological diagnosis of lymphoma

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Case Report

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Abstract

Background

Large B-cell lymphoma (LBCL) with interferon regulatory factor 4 (IRF4) rearrangement (IRF4+LBCL) is a rare and newly discovered subtype of mature B cell neoplasms.

Case presentation

Here, we describe a patient of 32 years old who was diagnosed IRF4+LBCL. Histological examination showed the normal structure of the lymphoid tissues were destroyed, and slightly crowded follicular or nodal structures instead. There were obvious necrosis on the surface of tonsil and the central part of some follicles. The monomorphic atypical lymphoid cells proliferated and grew consistently, which were of medium size or large, and the nuclear chromatin was opening. Some tumor cells can be seen around the normal striated muscle tissues near the tonsils. Immunohistochemistry (IHC) could show that CD20, CD79a, MUM-1 and BCL6 were positive, Ki-67 was 80%; CD3, CD5, CD10, BCL2, CD30, CD56, CD99, CD38, and CD138 were negative. In situ hybridization (ISH) of EBER was negative. Fluorescence in situ hybridization (FISH) confirmed that IRF4 gene rearrangement was found in tumor cells. The patient was followed up for 18 months without tumor after chemotherapy.

Conclusion

Generally speaking, destructive growth patterns with a large number of necrosis, high proliferation index and so on all suggest that the tumor is highly invasive. And in terms of pathological morphology, IRF4+LBCL can be similar to both high-grade follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). But actually this disease is indolent and significantly different.

Introduction

As a special type of mature B-cell tumor, IRF4 + LBCL is rare, accounting for 0.05% of LBCL[1]. In terms of immunophenotypic, the atypical tumor cells have mature B cell phenotype, what CD20, CD79a and PAX 5 are positive. The most characteristic is the cells strong express IRF4/MUM1 [1, 2, 3, 4]. Usually, Bcl 6 is positive, but CD10 and BCL2 are expressed in different degrees. The proliferation index is usually very high, and the expression pattern of Ki-67 shows the neoplastic follicles lack the polarity of normal lymphoid follicles or reactive proliferating follicles. In most IRF4 + LBCL, the tumor cells showed a complex pattern of genetic change, and most cases were found to have the origin of germatogenic center B cells, including the loss of TP 53 in a group of age-independent patients [1, 3, 4, 5]. And IgH with IRF4 gene translocation can be detected [1, 5]. Light chains are rarely involved in translocation. BCL 6 point breakpoints can be seen in some cases. However, almost all cases lacked MYC and BCL2 rearrangement [4, 6, 7]. Patients had good curative effect after combined immunochemotherapy, that was different from Paediatric-type follicular lymphoma, which could have a good prognosis without radiotherapy or chemotherapy.

Materials And Methods

The specimen was fixed with 10% neutral formalin solution, conventional dehydration, transparency, paraffin embedding, sliced thickness 4 μm , and the dyeing was carried out by using the HE method. In addition, the thin sections were resected 2 μm thick and stained with HE to observe the details of tumor cells. The EnVision method was used in immunohistochemistry. The first antibodies used were CD20, CD79a, CD3, CD5, CD45RO, CD21, CD23, MUM-1, BCL6, BCL2, CD10, CyclinD1, TDT, CD99, CD38, CD138, Ki-67, purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd and Fuzhou Maixin Biotechnology Co., Ltd. IRF4 isolated breakapark FISH probes was used for gene detection and purchased from ZytoVision Company of Germany.

Results

Clinical history

Male, 32 years old, the tumor is located in the left tonsil. During the onset the patient was snoring occurred more than 20 days ago without obvious inducement, occasionally sore throat, and obvious when swallowing and drinking water. No dysphagia, no itchy pharynx, no cold fever, no nausea and vomiting, no abdominal pain and abdominal distention, no cough and expectoration, no chest tightness and shortness of breath, no dyspnea, no earache, no ear pus. The family members of the patient did not pay attention to this at first, and he did not receive special treatment. However, the symptom of snoring had not be significantly better. Recently, the snoring was aggravated, lasted for a long time and snored louder, so they came to the outpatient department of our hospital to see a doctor. The results showed that the pharyngeal mucosa was ruddy, the soft palatal mucosa was not hypertrophic and relaxed, the uvula was in the middle, no lymphoid follicular hyperplasia was found in the posterior wall of pharynx, the left tonsil was enlarged and the recess was clean.

Pathologic findings

Under microscope, the tumor was mainly follicular pattern, and a large number of irregular follicles grew by pushing and extruding (Fig. 1). Some of the follicular structures were large and expansive, pushing the surrounding tissues, some of which with a starry sky phenomenon, but no polarity. The mantle zone disappears or becomes narrower and longer. High power, the tumor cells were medium size or large, abundant cytoplasm, irregular nuclei, chromatin vacuole. Basophilic nucleolus can be seen, and also mitotic images. Some tumor cells were looking like centroblasts which have one or more small nucleolus close to the nuclear membrane, and mitosis easy to found (Fig. 2). And also some areas of the tumor grew diffusely and showed a small amount of necrosis. Reactive lymphoid tissues were seen around the tumor.

Immunohistochemical test

Tumor cells expressed mature B cell markers, including CD20 and CD79a. MUM1 was strongly positive (Fig. 3). CD21 and CD23 showed a few disordered and broken follicular dendritic nets. BCL6 was focally positive, but CD3, CD5, CD45RO, CyclinD1, TDT, CD138 were all negative, EBER was also negative and the Ki67 index was about 80% (Fig. 4).

FISH test result

Most of the tumor cells could be found a single yellow signal appeared in the nuclear of tumor cells, and an orange and a green signal were isolated, what was suggesting IRF4 gene rearrangement (Fig. 5).

Treatment and prognosis

The patients received complete remission after R-CHOP regimen chemotherapy. Follow-up 18 months, so far no recurrence, but need more long-term follow-up data.

Discussion

IRF4 is a transcription factor that controls some important links in the development and maturation of B lymphocytes, including pre-B cell differentiation, marginal B cell development, germinal center reaction and plasma cell differentiation. A variety of transcriptional networks regulated by IRF4 in different B cell development stages and related malignant tumors are involved in the regulation of multiple genes. Therefore, the expression of IRF4 is involved in the proliferation and differentiation of B cells and the transformation of some lymphoid proliferating diseases [6–10]. Most IRF4 + LBCL occurs in the Waldeyer ring, and most patients have isolated lymph node enlargement in the head and neck, or tonsillar enlargement (clinical stage is I-II stage). L. de Leval and C. Bonnet et al [11] analyzed the cohort of WR DLBCL patients with DLBCL primary involved in Waldeyer ring. It found that WR DLBCLs had obvious clinicopathological features compared with conventional DLBCL, often accompanied by localized lesions and follicular growth. It has also been reported that IRF4 + LBCL tumor involves gastrointestinal tract [6, 7, 12]. It occurs mainly in children and young people, men are more common, but the reason is unknown. It also found that the prognosis of germinal center B cells, including FL and DLBCL, depends to a large extent on age [13–16]. The prognosis of children group is better than that of adult group. The characteristic change is the strong expression of the immunohistochemical IRF4/MUM1. Gene detection is usually accompanied by rearrangement of IRF4. Although tumor cells are characterized by high heterogeneous nucleus, and the proliferation index is usually high, but their prognosis is good. We must be familiar with its clinicopathological features, and that is helpful for diagnosis and differential diagnosis, avoiding misdiagnosis and causing overtreatment.

Our case shows that the patient was a man, the tumor occurred in the left tonsil and had a good prognosis, which is identical to the literatures.

Differential diagnosis:

1. paediatric-type follicular lymphomas (PTFL): It mainly involves Waldeyer ring or head and neck lymph nodes, and in the early age group, so it is the diseases that need to be identified the most. Pathologically, tumors are follicular growth patterns, and follicles are usually very large, with back-to-back growth patterns [6, 17–20]. The difference is that the tumor follicles of IRF4 + LBCL generally lack creeping morphology, and the positive expression of MUM1 was detected by immunohistochemistry and the abnormality of the IRF4 gene was detected by molecular detection can be identified.
2. Burkitt lymphoma: It mainly occurs in children, which is highly invasive lymphomas. A starry phenomenon characterized by pathological morphology. The Ki-67 index is high and close to 100%. It is of the central type of generation, CD10 is positive, and bcl2 is negative. The tumor cells are MYC and EBER positive, and genetic detection can be distinguished from IRF4 + LBCL.
3. High-grade FL and DLBCL: Most of the tumors occur in the elderly, and the clinical prognosis is poor. The tumor cells have large volume, obvious heteromorphism, high invasive growth and high proliferation index. Mature B cell antibodies are expressed in tumor cells, and MUM1 is always positive. It is very important to make differential diagnosis in contact with clinical data.

Conclusion

The frequency of IRF4 + LBCL is very high in children, especially in men. In pathological morphology, most of them are follicular growth pattern, but also can be completely diffused growth, and also can have both. The positive expression of IRF4/MUM 1 is constant and strong, and IRF4 rearrangement could be found by gene detection. Although it is a malignant tumor and has a high proliferation index, it has a good prognosis. IRF4 + LBCL is rare, its biological origin and the causes of multiple male children, etc. need more research to explain.

Abbreviations

DLBCL, diffuse large B-cell lymphoma; FISH, fluorescence in situ hybridization; FL, follicular lymphoma; LBCL, large B-cell lymphoma; IHC, Immunohistochemistry; IRF4, interferon regulatory factor 4; IRF4 + LBCL, large B-cell lymphoma with IRF4 rearrangement; ISH, In situ hybridization.

Declarations

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee.

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Conflict of Interest

The authors declare that they have no conflicts of Interest.

Contributions

Minya Lu performed experiments, analyzed data, and wrote the manuscript; Lisong Teng provided clinical data; Zhe Wang ,Xiaodong Teng and Zhaoming Wang contributed to designed research and analyzed data.

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None.

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Disclosure of conflict of interest

None.

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Figures

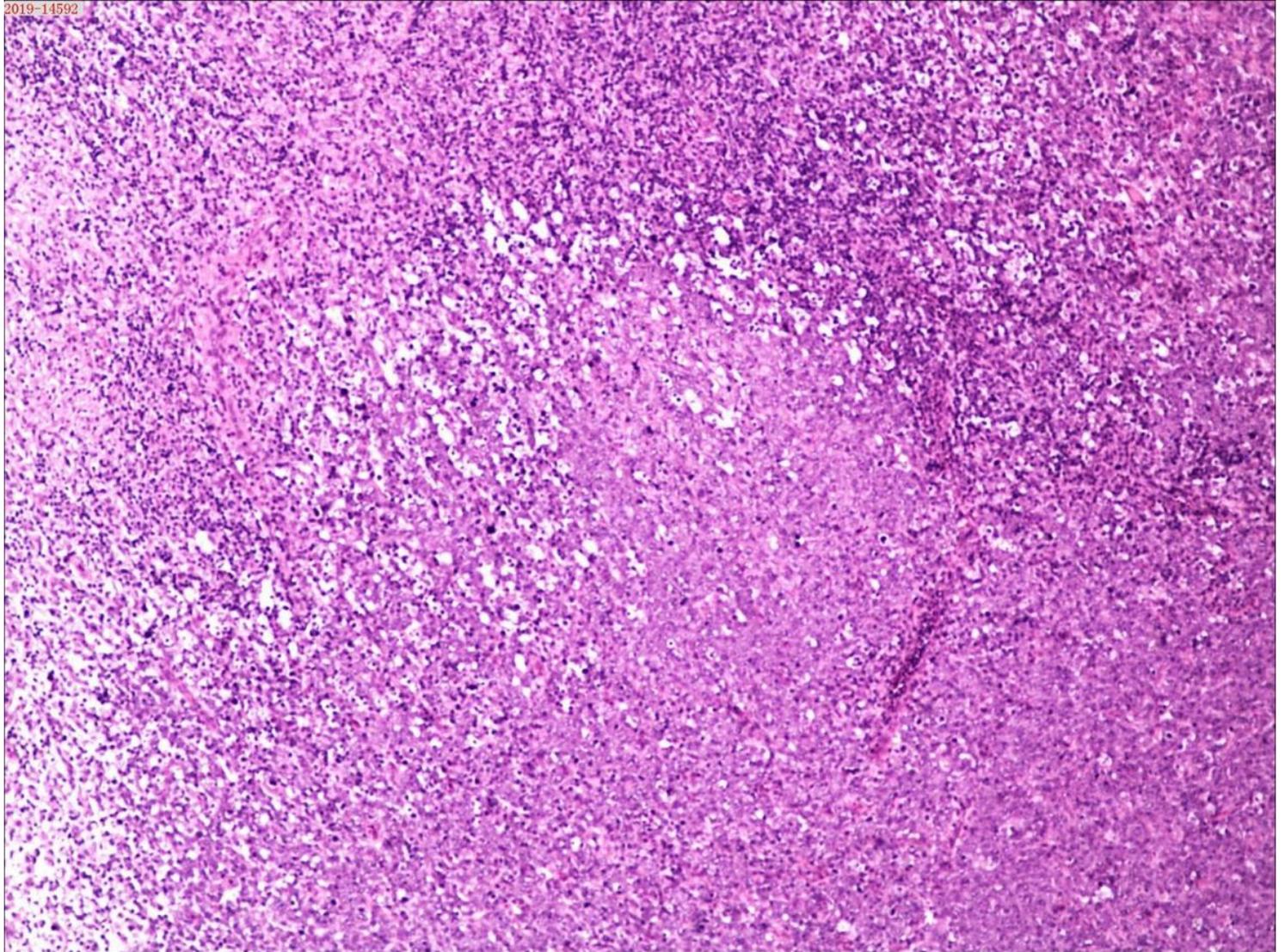


Figure 1

HE*100 Irregular follicles grow by pushing and extruding.

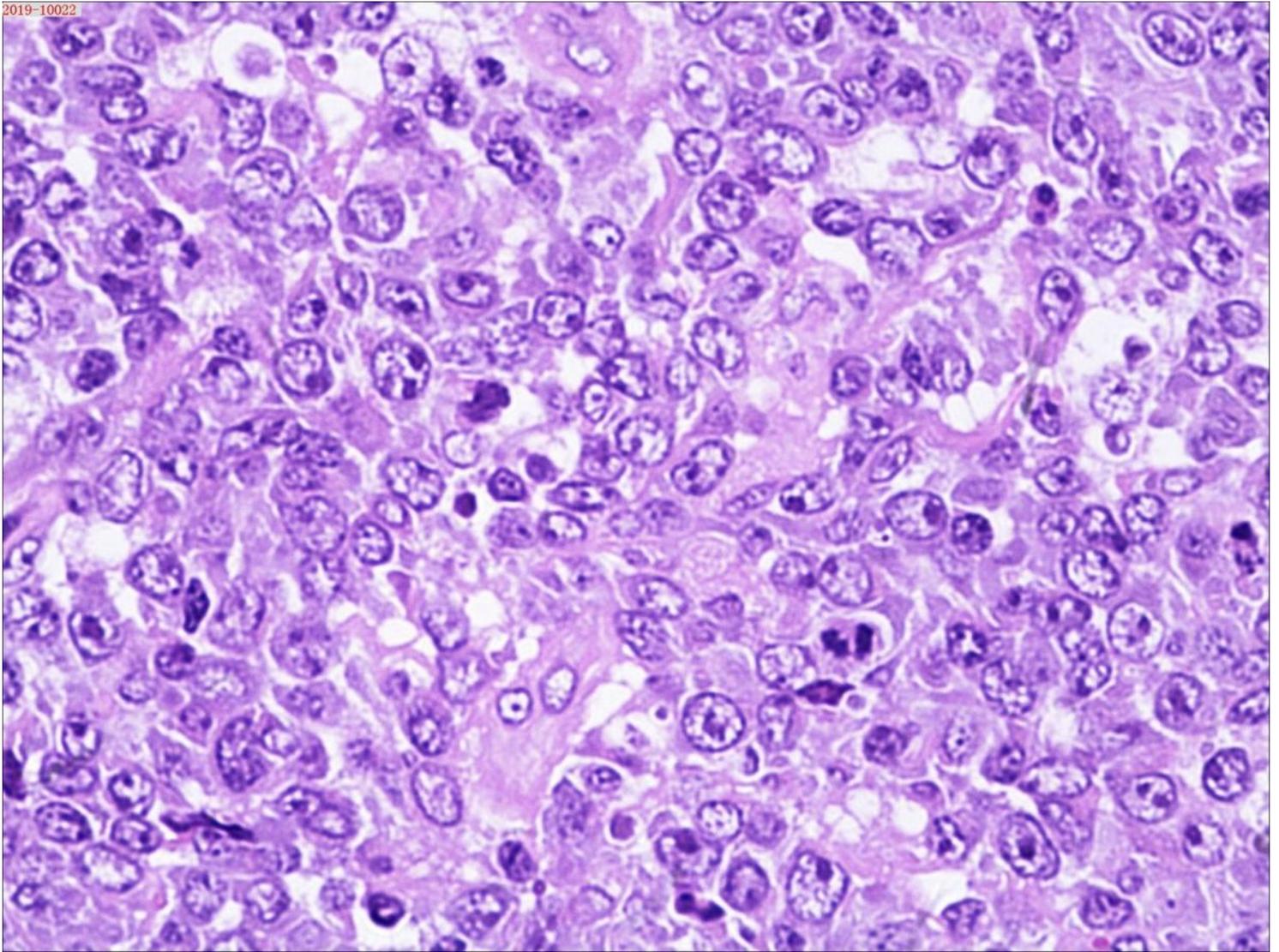


Figure 2

HE*400 some tumor cells have one or more small nucleolus close to the nuclear membrane.

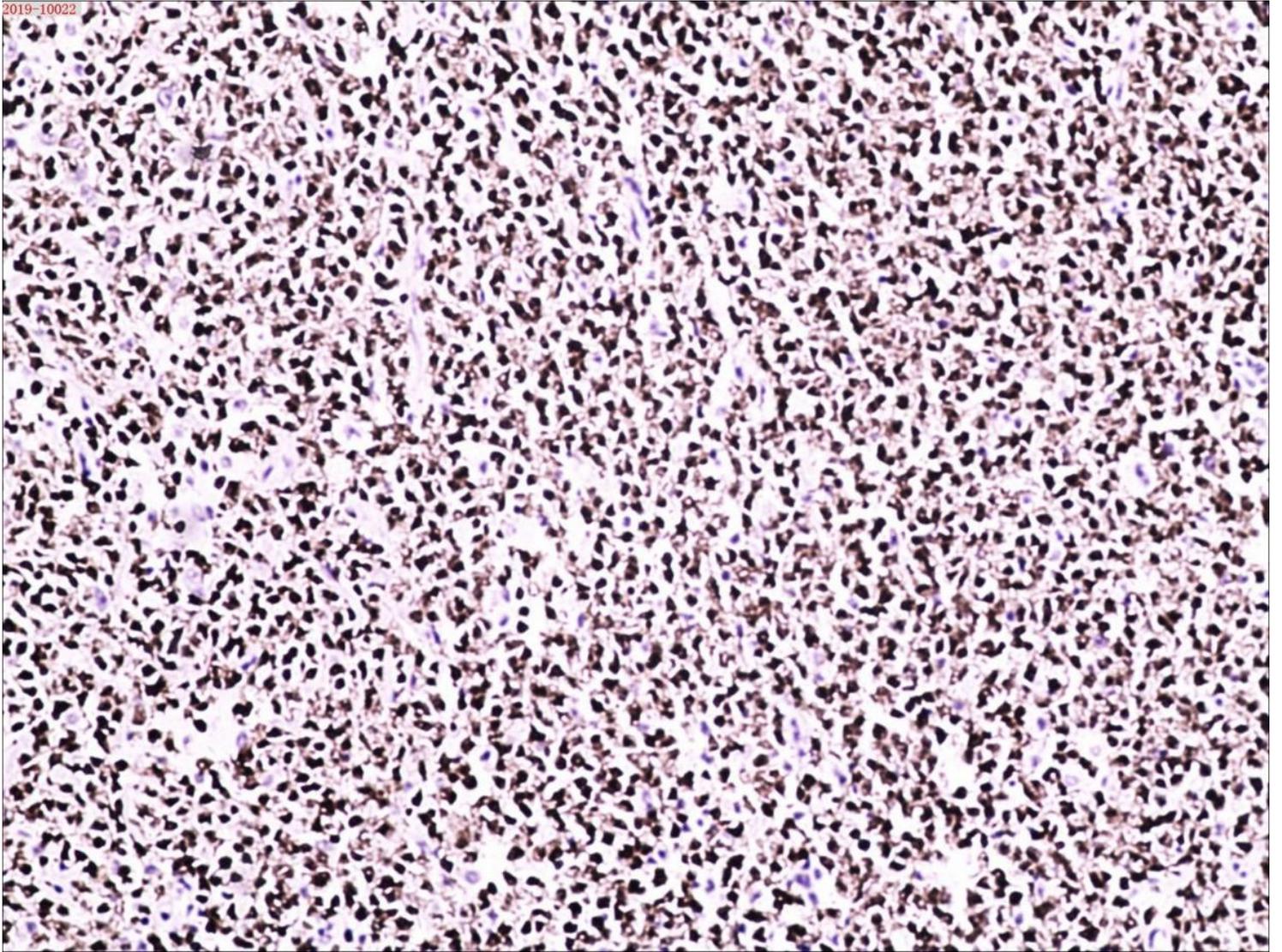


Figure 3

Evison*100 MUM1 is positive.

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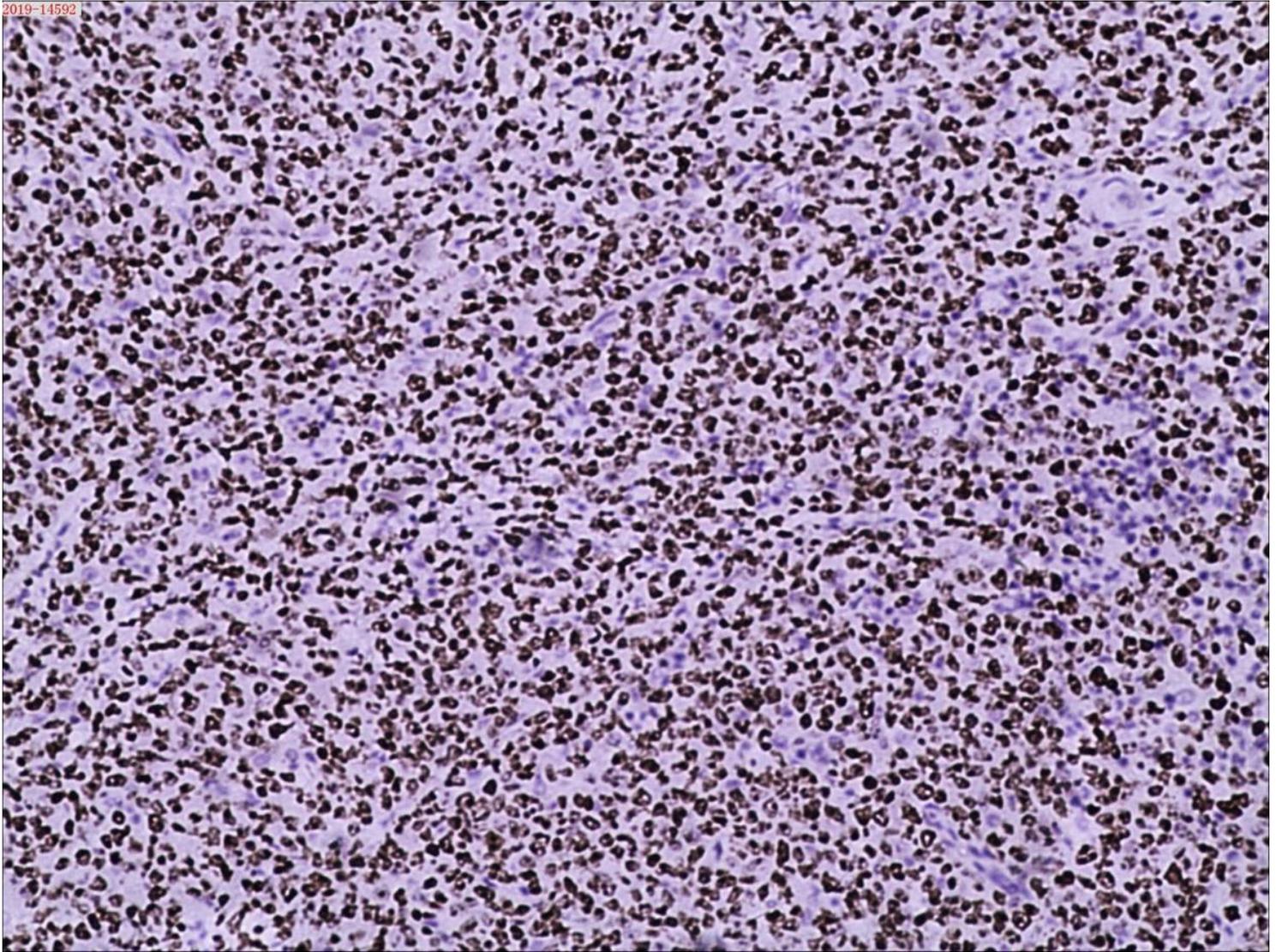


Figure 4

Evison*100 Ki67 is about 80%.

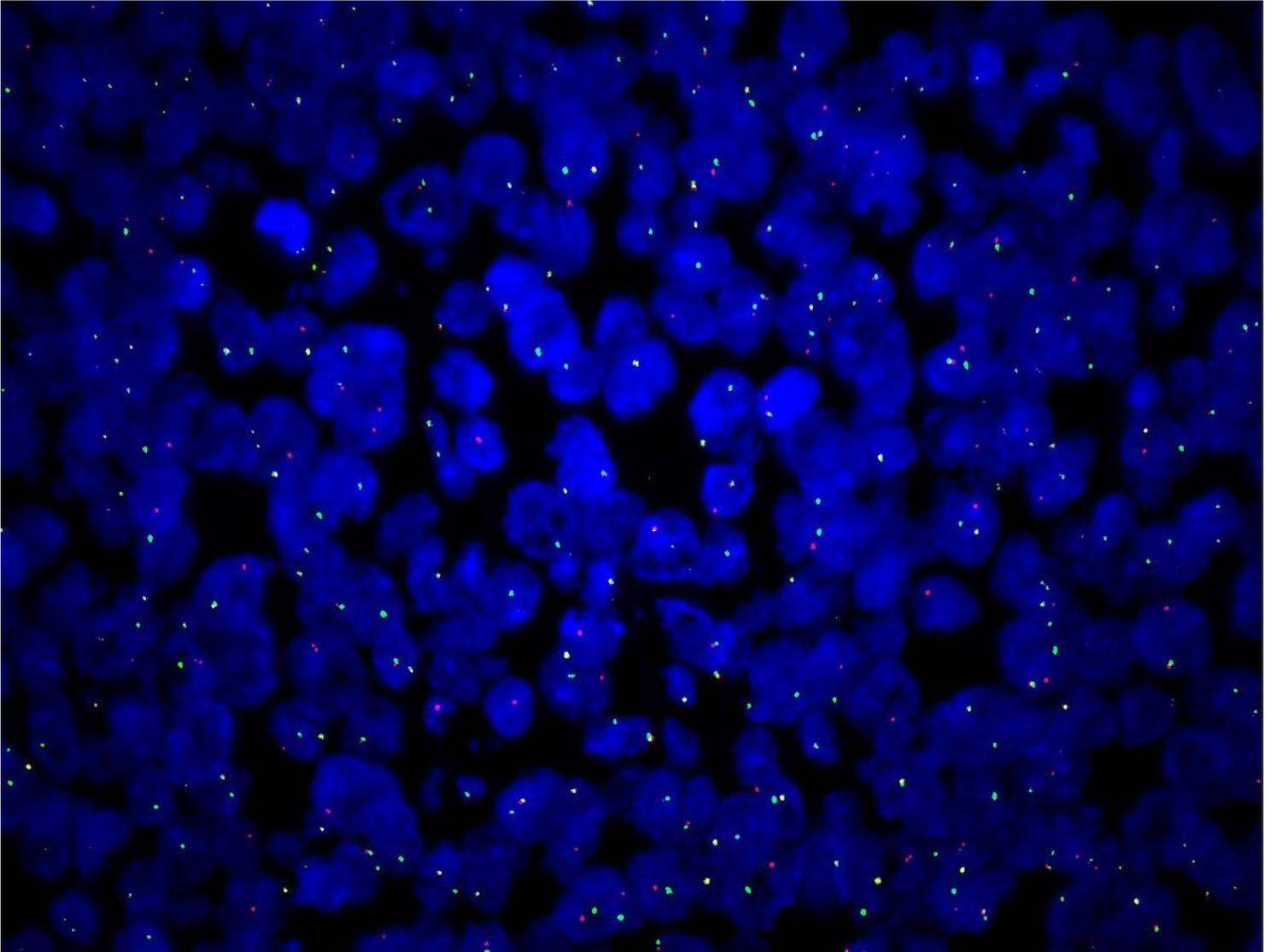


Figure 5

FISH IRF4 is arrangement.

Supplementary Files

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