Hairy cell leukemia (HCL) and hairy cell leukemia variant (HCL-v)

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Here you can learn about the classification and diagnostics of hairy cell leukemias and learn more about prognosis and therapy. In addition, we inform you about Hairy cell leukemia variant.

Diagnostic recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	mandatory
Chromosome analysis	-	no
FISH	-	no
Molecular genetics	EDTA or Heparin	mandatory

Definition and characteristics of Hairy cell leukemia

Hairy cell leukemia (HCL) is a rare disease, which is usually indolent. The incidence is 0.3/100,000 persons. The main age of onset of the disease is about 50 years. Men fall ill four to five times more frequently than women. Clinically, the disease is usually characterized by pronounced splenomegaly and pancytopenia. Characteristic is the appearance of hairy cells, with fine, hairy-like cytoplasmic spurs.

Classification of Hairy cell leukemia and Hairy cell leukemia variant

According to the WHO classification 2017, hairy cell leukemia belongs to the mature B-cell neoplasms. The central molecular genetic finding today is the *BRAF* mutation V600E, which is detectable in practically all patients with classic hairy cell leukemia and is helpful in differentiating it from other indolent non-Hodgkin lymphomas. According to the new WHO classification, the variant form of hairy cell leukemia (HCL-v) must be distinguished from hairy cell leukemia (see Table 1).

Table 1: WHO 2017 classification of hairy cell leukemia (HCL) and the variant form of hairy cell leukemia (HCL-v) (Swerdlow et al. 2017)

Mature B-cell neoplasms	
Hairy cell leukemia (HCL)	*BRAF* V600E-mutant mature memory B-cell
Hairy cell leukemia variant (HCL-v)	Wildtype *BRAF*

Hairy cell leukemia and its variant form differ especially in clinical and genetic aspects. Patients with HCL-v are older compared to patients with classic hairy cell leukemia, and men are similarly more likely to develop the disease than women (Matutes et al. 2001). However, the most important diagnostic difference is the absence of a *BRAF* mutation. In contrast to classical hairy cell leukemia, HCL-v shows a more aggressive course with shorter survival times and poorer response to conventional therapy approaches. Despite similarities in phenotype and immunophenotype, there are also differences (see Diagnostics).

Facts

>90%

of HCL patients have a *BRAF* V600E mutation

(Oncopedia Guideline HCL)

Hairy cell leukemia and Hairy cell leukemia variant - Diagnostics

Cytomorphology

As for all mature B-cell neoplasms, the methods of cytomorphology and histology are trend-setting for the control of downstream diagnostics.

In both the classic and the variant form of hairy cell leukemia, leukemia cells are found in the bone marrow and spleen, and leukemia outflow into the peripheral blood is low in HCL and pronounced in HCL-v (Swerdlow et al. 2017). Characteristic in cell morphology are the hair-like cytoplasmic outgrowths that give the cells their name. HCL-v cells have morphological characteristics that are located between hair cells and prolymphocytes. They have distinct nucleoli as an essential distinguishing feature for morphological differentiation from classical hair cells. However, immunophenotyping plays a major role in the differentiation between HCL and HCL-v (Grever et al. 2017).

The examination of the bone marrow aspirate and especially the -biopsy is essential to determine the extent of bone marrow infiltration and to validate the diagnosis (Grever et al. 2017). In HCL, aspiration is often unsuccessful because of reticulin fibrosis of the marrow ("punctio sicca"). However, fibrosis is not observed in HCL-v (Swerdlow et al. 2017).

Immunophenotyping

Annexin A1 and CD103 are specific markers for hairy cell leukemia

Specific for hairy cell leukemia is the immunohistochemically detectable expression of Annexin A1 (*ANXA1*), which is not found in any other mature B cell neoplasm. Furthermore, the expression of CD103, CD11c and CD25 is observed in immunophenotyping. In contrast to classical hairy cell leukemia, no expression of CD25 and Annexin A1 is detectable in HCL-v. This very specific expression pattern can be used very well and with high sensitivity to measure the minimal/measurable residual disease (MRD).

Table 2: Characteristic findings in hairy cell leukemia according to Béné et al. 2011

Antigene	Result
CD19	+
CD20	+
CD22	+
CD23	+/-
CD25	+
FMC7	+
CD79b	+
CD5	+/-
sIg	(+)
CD10	+/-
CD11c	+
CD103	+

Chromosome analysis

Chromosome analysis is not obligatory in the diagnosis of hairy cell leukemia. Due to the low in vitro proliferation of HCL or HCL-v cells, there are also only few data on cytogenetic abnormalities.

For hairy cell leukemia, a broad spectrum of chromosomal abnormalities has been described affecting chromosomes 1, 2, 5, 6, 7, 11, 13, 14, 19, 20 (Haglund et al. 1994, Kluin-Nelemans et al. 1994, Hockley et al. 2011, Durham et al. 2017). Thereby deletions and inversions seem to occur more frequently than numerical aberrations or translocations (Haglund et al. 1994). Cytogenetic abnormalities may also affect the IGH locus on 14q32 (Kluin-Nelemans et al. 1994). However, none of the described chromosome abnormalities is specific for hairy cell leukemia.

For the variant form of hairy cell leukemia various numerical and structural chromosomal alterations up to the complex karyotype are found as well (Brito-Babapulle et al. 1994, Angelova et al. 2018). In some cases, rearrangements involving the loci of immunoglobulins are also observed (Brito-Babapulle et al. 1994, Matutes et al. 2001).

FISH

Like chromosome analysis, this examination is not obligatory for the diagnosis of HCL and HCL-v. By using different techniques for the analysis of copy number changes, 17p-deletions (*TP53*) as well as 11q-deletions (*ATM*) could be described especially for the variant form of hairy cell leukemia (Dierlamm et al. 2001, Hockley et al. 2011), which can also be detected by FISH (Matutes et al. 2001, Angelova et al. 2018).

Molecular genetics

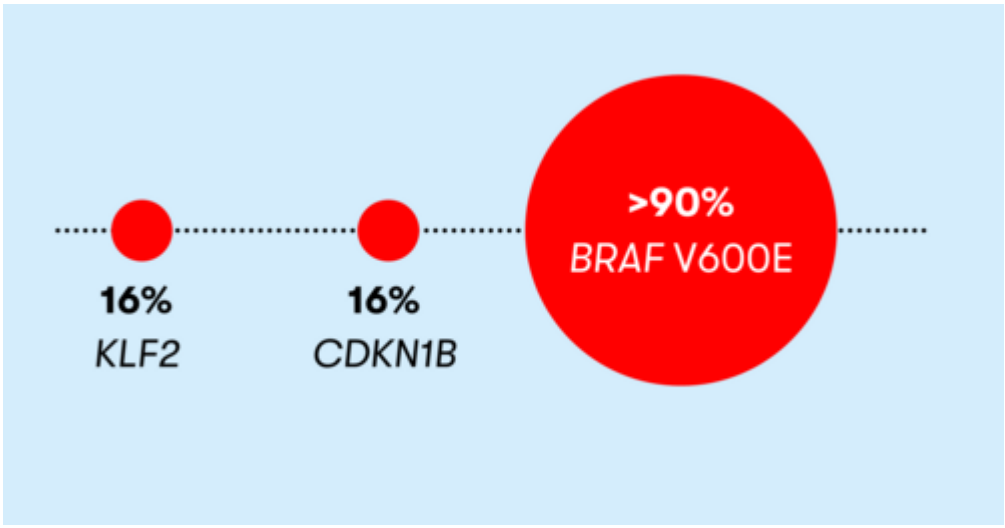
***BRAF* mutation V600E is most specific for hairy cell leukemia**

In hairy cell leukemia, the V600E mutation in the *BRAF* gene is of great importance. This point mutation occurs in over 90% of patients with hairy cell leukemia, but is extremely rare in other mature B-cell neoplasms (Tiacci et al. 2011, Blombery et al. 2012). This can greatly facilitate the differentiation of hairy cell leukemia from other lymphomas (especially HCL-v and SMZL). However, the slight blurring of the marker may also be caused by the methodological limitations of the previous gold standards. Furthermore, the quantification of the *BRAF* V600E mutation by real-time PCR can be used very well and with high sensitivity as a progression marker (MRD) (Schnittger et al. 2012).

The BRAF protein (encoded by the *BRAF* proto-oncogene on chromosome 7q34) is a member of the serine/threonine kinase RAF family and a key component of the RAS-RAF-MEK-ERK signaling pathway. The V600E mutation in the *BRAF* gene leads to a permanent activation of the pathway and thus represents the key event in the molecular pathogenesis of hairy cell leukemia (Tiacci et al. 2011, Falini et al. 2016). For the majority of patients (>85%) somatic hypermutations of the IGHV locus are detectable (Swerdlow et al. 2017).

For cases without detectable *BRAF* mutation but with the classic HCL phenotype and immunophenotype, an association with the IGHV4-34 gene appears to exist (Maitre et al. 2019) and there is evidence that IGHV4-34 expression and BRAF mutation are mutually exclusive (Xi et al. 2012, Waterfall et al. 2014). IGHV4-34 positive classical hairy cell leukemia is associated with an unmutated IGHV status, a less favorable prognosis and a reduced response to therapy with purine analogues (Arons et al. 2009, Forconi et al. 2009, Xi et al. 2012). In some of these cases, mutations in the MAP2K1 gene, which encodes the MEK1 kinase, which also plays a key role in the RAS-RAF-MEK-ERK pathway, have been described (Waterfall et al. 2014, Maitre et al. 2018).

Figure 1: Common mutations in hairy cell leukemia



CDKN1B and _KLF2_ mutations second most common in hairy cell leukemia
Mutations in the *CDKN1B* gene represent other common molecular genetic mutations, which are observed in 16% of patients with hairy cell leukemia (Dietrich et al. 2015). *CDKN1B* mutations also occur together with *BRAF* mutations. Although they do not affect the prognosis of patients, they appear to play an important role in the pathogenesis of hairy cell leukemia (Dietrich et al. 2015). In addition, mutations in *KLF2*, a transcription factor involved in homeostasis and differentiation of B cells, were also found with a frequency of 16% (Piva et al. 2015, Falini et al. 2016).

Mutations in the variant form of hairy cell leukemia
As for classical hairy cell leukemia, the majority of patients with HCL-v (71-73%) have somatic hypermutations in the IGHV locus (Hockley et al. 2010, Hockley et al. 2012). Among the cases with unmutated IGHV, the IGHV4-34 gene is found preferentially (Hockley et al. 2010). Mutations in the *TP53* gene are also associated with an unmutated IGHV status (Hockley et al. 2012, Swerdlow et al. 2017).

Studies on the molecular genetic characterization of the classic and variant form of hairy cell leukemia also showed an association with *MAP2K1* mutations for HCL-v in up to 42% of cases (Waterfall et al. 2014, Durham et al. 2017, Maitre et al. 2018, Maitre et al. 2019). Further mutations have been described in the genes *CCND3*, *U2AF1* and the epigenetic factors *KMT2C*, *KDM6A*, *CREBBP* and *ARID1A* (Durham et al. 2017, Maitre et al. 2018, Maitre et al. 2019).

Prognosis of Hairy cell leukemia

The majority of patients with hairy cell leukemia have a normal life expectancy
Classical hairy cell leukemia has a good prognosis in the majority of patients and about 70% of patients have a normal life expectancy (Onkopedia Guideline HCL 2020). The decisive factor is the response to therapy. Patients who achieve complete remission have a significantly better prognosis compared to patients with partial remission (e.g. Else et al. 2009, Rosenberg et al. 2014, Grever et al. 2017, Onkopedia Guideline HCL 2020). It is still controversial whether the risk of secondary tumors is increased (e.g. Maitre et al. 2019). In contrast to classical hairy cell leukemia, HCL-v shows a more aggressive course with shorter survival times (Swerdlow et al. 2017).

Therapy of Hairy cell leukemia

Frequent recurrence despite initial high response rate
The therapy of patients with hairy cell leukemia is usually carried out with purine nucleoside analogues (cladribine, pentostatin), which can also be given in combination with anti-CD20 monoclonal antibodies (rituximab) if necessary (Grever 2010, Grever et al. 2017). Thus, for ~80 - 85% of the patients a permanent complete remission of the disease can be achieved over several years, even if a relapse occurs in about 40 - 50% of the patients (Grever 2010).

New targeted treatment options, especially for patients with relapse, include the use of *BRAF* and MEK inhibitors (vemurafenib, dabrafenib, trametinib) that inhibit the RAS-RAF-MEK-ERK signaling pathway overactivated by the BRAF V600E mutation. In two clinical trials with vemurafenib, very good response rates were achieved (overall response 96% and 100%, complete remission at 35% and 42%, respectively) (Tiacci et al. 2015, Falini et al. 2016). However, these patients also showed a high rate of recurrence due to the development of resistance to the BRAF inhibitors. Future therapeutic strategies should therefore focus on reducing the development of resistance, for example by using new BRAF inhibitors, combining *BRAF* and *MEK* inhibitors or combining *BRAF* inhibitors with anti-CD20 monoclonal antibodies (Falini et al. 2016). Further therapeutic approaches for relapsed/refractory hairy cell leukemia are the immunotoxin moxetumomab pasudotox, which is directed against CD22, and the bruton tyrosine kinase inhibitor ibrutinib (Maitre et al. 2019).

For patients with the variant form of hairy cell leukemia, the overall response to cladribine monotherapy was below 50%, with a complete remission rate of 8% (Kreitmann et al. 2013). However, by combining cladribine with the anti-CD20 antibody rituximab, the proportion of complete remissions could be increased to 86% when administered sequentially (Chihara et al. 2016) and to 90% when given in combination (Kreitmann et al. 2013). Cladribine/rituximab therapy is therefore currently recommended as first-line therapy (Maitre et al. 2019). Therapeutic options for relapsed/refractory HCL-v include: a repetition of cladribine/rituximab therapy, participation in clinical trials, treatment with moxetumomab pasudotox and treatment with ibrutinib (as monotherapy or combination therapy with the *BCL2* inhibitor Venetoclax) (Maitre et al. 2019).

References

You can find the corresponding references here: