CHIP in hematology (clonal hematopoiesis of indeterminate potential)

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Continuous research and targeted examinations of blood and bone marrow result in various diagnostic recommendations for patients with CHIP in hematology. Further information about CHIP in Cardiology can be found **here (clonal hematopoiesis of indeterminate potential)**.

Diagnostic recommendation

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

CHIP hematology - definition and characteristics

Clonal hematopoiesis of indeterminate potential (CHIP) refers to the presence of clonal molecular genetic or cytogenetic changes in blood or bone marrow cells in the absence of signs of hematological neoplasm and absence of cytopenia. The incidence of CHIP increases with age. While CHIP was detected only in rare cases in persons under 40 years of age, clonal hematopoiesis has been detected in about 10% of persons from the age of 70 onwards. Similar to patients with **MGUS** (monoclonal gammopathy of unclear significance) or with **MBL** (monoclonal B-cell lymphocytosis), individuals with CHIP showed an increased risk of developing hematological neoplasm. This risk was 11 to 13 times higher in individuals with clonal hematopoiesis, but the overall transformation rate was relatively low at 0.5-1% per year.

Classification of CHIP hematology

CHIP was introduced as a new term only a few years ago (Steensma et al. 2015). Through large studies of a total of more than 30,000 blood samples it could be shown that in some cases gene mutations exist in persons with inconspicuous blood counts, which had previously been detected mainly in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) (Genovese et al. 2014, Jaiswal et al. 2014, Xie et al. 2014). The genes *DNMT3A*, *TET2* and *ASXL1* were most frequently affected.

Characteristics of CHIP (after Steensma et al. 2015)

- Evidence of clonal hematopoiesis*
- Absence of dysplasia of hematopoiesis in bone marrow
- No proliferation of blasts in bone marrow/blood
- Exclusion of paroxysmal nocturnal hemoglobinuria (PNH), MGUS and MBL
- Progression rate of 0.5-1% per year

*somatic mutation with an allelic frequency of at least 2% in one of the genes: *DNMT3A*, *TET2*, *JAK2*, *SF3B1*, *ASXL1*, *TP53*, *CBL*, *GNB1*, *BCOR*, *U2AF1*, *CREBBP*, *CUX1*, *SRSF2*, *MLL2* (*KMT2D*), *SETD2*, *SETDB1*, *GNAS*, *PPM1D*, *BCORL1* or a non-disease-defining clonal cytogenetic alteration

Delineation from CCUS and MDS
In addition to CHIP, CCUS (clonal cytopenia of indeterminate significance), ICUS (idiopathic cytopenia of indeterminate significance) and IDUS (idiopathic dysplasia of indeterminate significance) are possible preliminary stages of MDS.

If clonal haematopoiesis is also accompanied by cytopenia, this is referred to as CCUS. CHIP and CCUS differ from ICUS and IDUS by the evidence of clonality. In IDUS, as in MDS, dysplasia is also present.

Table 1: Pre-MDS and MDS conditions: typical features and criteria, according to Valent et al. 2017

	CHIP	CCUS	ICUS	IDUS	LR MDS	HR MDS
Monoclonal/Oligoclonal	+	+	-/+	+/-	+	+
Dysplasia*	-	-	-	+	+	+
Cytopenia(s)**	-	+	+	-	+	+
BM blasts	<5%	<5%	<5%	<5%	<5%	<20%
Flow abnormalities	+/-	+/-	+/-	+/-	++	+++
Cytogenetic abnormalities	+/-	-	+/-	+/-	+	++
Molecular aberration/s	+	+	-	-	++	+++

*At least 10% of all cells in a given lineage (erythroid, neutrophil, or megakaryocyte) are dysplastic.

**Persistent cytopenia(s) recorded over a time-period of at least 4 months.

CHIP hematology - Diagnostics

Cytomorphology

If clonal hematopoiesis is present due to the molecular genetic or cytogenetic findings, CHIP hematology (absence of dysplasia and cytopenia) should be distinguished from CCUS (cytopenia, but absence of dysplasia) or myeloid neoplasia in a cytomorphological examination.

Chromosome analysis

Clonal hematopoiesis can also be diagnosed in the absence of somatic mutations due to non-disease-defining clonal cytogenetic changes.

FISH

If it is not possible to perform a chromosome analysis, FISH can also be used to detect clonal haematopoiesis.

Molecular genetics

Difficult to differentiate CHIP vs. MDS

The sole detection of a mutation in one of the genes frequently mutated in AML and MDS does not allow a distinction to be made between CHIP and MDS **(see also Diagnostics MDS (molecular genetics))**. A smooth transition between CHIP and MDS is assumed to be probable. An important indication of this is the increase in genetic complexity (see Table 2) with regard to the number of mutations as well as clone size (allele frequency) (Cargo et al. 2015, Bejar 2017, Malcovati et al. 2017, Bewersdorf et al. 2019).

Table 2: Comparison of genetic characteristics between CHIP, CCUS and MDS, according to Bejar 2017

	CHIP (unselected population)	CCUS (at diagnosis)	MDS (all risk groups)
Commonly mutated genes	*DNMT3A*, *TET2*, *ASXL1*, *PPM1D*, *JAK2*, *TP53*	*TET2*, *DNMT3A*, *ASXL1*, *SRSF2*, *TP53*	*SF3B1*, *TET2*, *ASXL1*, *SRSF2*, *DNMT3A*
Mean # of Mutations	~1	~1,6	~2,6
Typical VAF	9-12%	30-40%	30-50%
Incidence	about 10-15% of 70 year-olds	about 35% of ICUS	may be <50% of cytopenic patients

Overall, MDS are molecularly more complex than CHIP: there are usually two or more mutations and the mutation load is usually above 10% (Haferlach et al. 2014, Malcovati et al. 2017, Sperling et al. 2017). In addition, mutations in certain genes (e.g. spliceosome factors) are found more frequently in MDS than in CHIP, see Table 2 (Bejar 2017). Since a progression (usually into MDS or AML, more rarely into myeloproliferative or lymphatic neoplasm) leads to an accumulation of several mutations (e.g. Steensma et al. 2015), it is recommended to perform follow-up examinations in questionable cases.

Table 3: Somatically mutated genes detectable in patients with MDS and CHIP (Valent et al. 2017)

Table 3 shows an overview of known mutations in MDS and CHIP. The presence of multiple mutations (e.g. *SF3B1*, *SRSF2*) increases the probability of an MDS diagnosis or that the patient will develop MDS.

Gene	Chromosome localisation	Frequency*	
		MDS	CHIP
NRAS	1p13.2	+/-	-
DNMT3A	2p23	+	+
SF3B1	2q33.1	+	+/-
IDH1	2q33.3	+/-	-
GATA2	3q21.3	-	-
KIT	4q11-12	+/-	-
TET2	4q24	+	+
NPM1	5q35.1	-	-
EZH2	7q35-36	+/-	-
JAK2	9p24	+/-	+
CBL	11q23.3	+/-	+/-
KRAS	12p12-11	-	-
ETV6	12p13	-	-
FLT3	13q12	-	-
IDH2	15q26.1	-	-
TP53	17p13.1	+/-	+/-
PRPF8	17p13.3	-	-
SRSF2	17q25.1	+	+/-
CEBPA	19q13.1	-	-
ASXL1	20q11	+	+
U2AF1	21q22.31	+/-	-
RUNX1	21q22.12	+/-	-
BCOR	Xp11.4	-	-
ZRSR2	Xp22.1	+/-	-
STAG2	Xq25	+/-	-

*Score of frequency:
- <1% of all patients
+/- 1-10% of all patients
+ >10% of all patients

Prognosis of CHIP hematology

Association between CHIP and hematological and cardiovascular diseases
Total exome sequencing (i.e. sequencing of all protein-coding genes) of more than 17,000 DNA samples from peripheral blood not selected for hematological diseases showed that age-related clonal hematopoiesis is associated with an increased risk of developing hematological neoplasm (Jaiswal et al. 2014).

Jaiswal and colleagues also found an association between CHIP hematology and increased mortality (Jaiswal et al. 2014), which, according to current knowledge, is due to an association between CHIP and cardiovascular diseases (Jaiswal et al. 2014 & 2017). Especially in the case of *TET2* mutations there are indications that faulty inflammatory reactions could be the cause (Jaiswal et al. 2017).

CHIP-associated mutations and mutation patterns differ in their predictive value for a progression into MDS or AML
The possible progression of clonal hematopoiesis into MDS was investigated in a large international study for patients with unexplained cytopenia of undetermined significance (CUS). The data provide first indications that the detection of mutations has a predictive value in this context. Patients in whom a mutation was detected had an approximately 14-fold increased risk of developing myeloid neoplasm. The occurring mutations or mutation patterns had different effects on the risk of progression. For patients with a mutation in one of the spliceosome genes (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*) or in one of the epigenetic factors *TET2*, *ASXL1* or *DNMT3A* in combination with another mutation, the risk was about 20% per year. In patients with a different mutation pattern, the risk was approximately 10% per year (Malcovati et al. 2017) (see also CCUS).

In two retrospective studies it was evaluated whether risk factors for the development of AML can be identified. Especially mutations in *TP53*, *IDH1/2* and spliceosome genes were associated with an increased risk of progression. Just as for a possible progression into MDS (see CHIP (molecular genetics)), an influence of clone size, the number of mutations as well as the kinetics of clonal expansion could be determined (Abelson et al. 2018, Desai et al. 2018).

CHIP hematology as a possible risk factor for the development of therapy-associated myeloid neoplasm
CHIP hematology clones can gain and expand a selective survival advantage under haematological stress, which can result from cytotoxic therapy, radiation or stem cell transplantation (Ortmann et al. 2019, Coombs et al. 2017, Wong et al. 2018). In particular, *TP53* and *PPM1D* mutant clones are associated with the development of therapy-associated neoplasms after cytotoxic therapy (Coombs et al. 2017, Hsu et al. 2018, Kahn et al. 2018, Wong et al. 2015 & 2018). Mutations of these two genes are found with a frequency of 4% each among the CHIP-associated mutations (Heuser et al. 2016).

Identification of CHIP possibly of future importance for stem cell transplantation
In a retrospective analysis, it was shown that patients with CHIP (CHIP hematology) after autologous stem cell transplantation for the treatment of lymphoma had an increased risk of developing therapy-associated myeloid neoplasm. Furthermore, overall survival was significantly reduced (Gibson et al. 2017).

However, in a first study of allogeneic stem cell transplantation, the CHIP hematology status of the donor did not affect the overall survival of the recipients (Frick et al. 2018). In the context of CHIP-positive stem cell donors, an increased incidence of chronic graft-versus-host disease was observed, which was associated with a lower rate of recurrence or progression (Frick et al. 2018). However, there are case reports on the occurrence of donor cell leukemia after allogeneic stem cell transplantation in connection with CHIP-positive older donors (Gondek et al. 2016, Frick et al. 2018).

CHIP hematology: Recommendation

Also in view of the lack of possibilities for therapeutic intervention, screening for the presence of a CHIP hematology is not recommended in persons with normal blood counts (Heuser et al. 2016). Often the detection of clonal haematopoiesis is a random finding. With a normal blood count, a differential blood count should be performed at regular intervals (initially after 3 months, later every 12 months) in patients with CHIP hematology in order to detect possible progression. If the patient has peripheral cytopenia, a bone marrow puncture and a differential blood count are recommended initially after 1, 2 and 3 months and subsequently every 3 months (Heuser et al. 2016).

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/others/clonal-hematopoiesis-of-indeterminate-potential-chip-in-hematology.html#references