Clonal hematopoiesis of indeterminate potential (CHIP in cardiology)

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

Diagnostic recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory in case of positive molecular genetics
Immunophenotyping	-	no
Chromosome analysis	-	no
FISH	-	no
Molecular genetics	EDTA or Heparin	mandatory

Definition and characteristics of CHIP cardiology

Clonal hematopoiesis of indeterminate potential (CHIP) is the presence of clonal genetic alterations in blood or bone marrow cells in the absence of signs of hematological neoplasia and absence of cytopenia. The incidence of CHIP increases with age. While clonal hematopoiesis of indeterminate potential was detected only in rare cases in persons under 40 years of age, clonal haematopoiesis 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 were found to be at increased risk of developing hematological neoplasia. 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. In comparison, a relevant correlation between the occurrence of clonal hematopoiesis of indeterminate potential and cardiovascular disease was shown.

Association between CHIP 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 revealed an association between clonal hematopoiesis and increased mortality linked to an increased risk of coronary heart disease and ischemic insult (Jaiswal et al. 2014). Further investigations confirmed the association between clonal hematopoiesis of indeterminate potential and cardiovascular disease.

CHIP and atherosclerosis
Clonal hematopoiesis of indeterminate potential was investigated in detail as a risk factor for cardiovascular diseases in several case-control studies with more than 8,000 subjects, taking into account classical cardiovascular risk factors (age, sex, diabetes mellitus, total cholesterol, HDL cholesterol, smoking, and hypertension) (Jaiswal et al. 2017). The risk for the occurrence of coronary heart disease was increased by a factor of 1.9 in the presence of CHIP; the risk for the early occurrence of myocardial infarction before the age of 45 or 50 was 4 times higher in the presence of CHIP (Jaiswal et al. 2017). The detailed analysis of different mutated genes showed a particularly high risk for *JAK2* mutations compared to the more frequent mutations in the genes *DNMT3A*, *TET2* and *ASXL1*. In volunteers who had not yet experienced an event of coronary artery disease, an association between CHIP and coronary artery radiographic calcification was documented, suggesting a role of CHIP in the progression of atherosclerosis (Jaiswal et al. 2017). Overall, the cardiovascular risk associated with CHIP is at least in a similar order of magnitude to established cardiovascular risk factors such as cigarette smoking, hyperlipidaemia or hypertension (Jaiswal et al. 2019 & 2020). In addition to epidemiological data, the role of CHIP in the pathogenesis of atherosclerosis was also investigated experimentally. Several studies in animal models showed that clonal hematopoiesis of indeterminate potential is causative for progression of atherosclerosis. Mechanistically, faulty inflammatory reactions of clonal blood cells are assumed to contribute to the cardiovascular endpoint. In particular, a proinflammatory phenotype has been described for *TET2* mutated or deficient monocytes/macrophages in atherosclerotic lesions (Fuster et al. 2017, Jaiswal et al. 2017). Furthermore, by blocking the interleukin-1β-mediated inflammatory response, a reduction of CHIP-associated atherosclerosis was achieved in the mouse model (Fuster et al. 2017).

CHIP and aortic valve stenosis
In a cohort of 279 patients with degenerative aortic valve stenosis without hematological disease, the influence of clonal hematopoiesis of indeterminate potential (CHIP) on overall survival after transcatheter aortic valve implantation (TAVI) was investigated. In the first 8 months after surgery, survival in patients with somatic mutations in the genes *DNMT3A* or *TET2* was significantly worse than in patients without such mutations (p=0.012). Overall, the mortality risk was 3.1 times higher in the presence of mutations in the genes *DNMT3A* or *TET2* (Mas-Peiro et al. 2020).

CHIP and heart failure
Another study examined the role of clonal hematopoiesis of indeterminate potential (CHIP) in a cohort of 200 patients with chronic heart failure after successfully revascularized myocardial infarction. CHIP was frequently detected in this patient group (18.5%) and was associated with significantly worse long-term survival (p=0.003). Also for a combined endpoint of death and rehospitalization due to heart failure (median observation period of 4.4 years) the data were significantly worse for patients with mutations in the genes *DNMT3A* and *TET2* than for patients without CHIP-associated mutations (p=0.001). This association of CHIP with impaired long-term survival and faster disease progression of ischemic heart failure was found despite no differences in the baseline extend of heart failure in the groups according to New York Heart Association (NYHA) classification, Seattle Heart Failure Model (SHFM) score, left ventricular ejection fraction, or serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Dorsheimer et al. 2019). Again, a causal relationship between *TET2* mutated or deficient proinflammatory monocytes/macrophages in the myocardium and the progression of ischemic heart failure with increased cardiac fibrosis and decreased ejection fraction was shown in animal models (Sano et al. 2018).

Classification of clonal hematopoiesis of indeterminate potential

Clonal hematopoiesis of indeterminate potential 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 leukaemia (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 clonal hematopoiesis of indeterminate potential (CHIP)

(according to Steensma et al. 2015)
- Evidence of clonal haematopoiesis*
- Absence of dysplasia of hematopoiesis in bone marrow
- No proliferation of blasts in bone marrow/blood
- Exclusion of paroxysmal nocturnal haemoglobinuria (PNH), MGUS and MBL
- Progression rate of 0.5-1% per year

*somatic mutation with an allelic frequency of at least 2% in any 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

Distinction of CHIP cardiology from CCUS and MDS
Clonal hematopoiesis of indeterminate potential is also a possible preliminary stage of myelodysplastic syndrome (MDS) or other hematological neoplasia, but has a comparatively low risk of progression (see **Clonal hematopoiesis of indeterminate potential (CHIP) in hematology**). If clonal haematopoiesis is accompanied by cytopenia, this is referred to as CCUS (**clonal cytopenia of undetermined significance**). CCUS is associated with a significantly higher risk of hematological progression than CHIP (Malcovati et al. 2017). CHIP-associated somatic mutations are also frequently detected in MDS (Haferlach et al. 2014). By definition, the full clinical picture of MDS includes dysplasia or a cytogenetic aberration typical of the disease in addition to cytopenia (Valent et al. 2017).

Table 1: Distinction of CHIP and CCUS from MDS, modified according to Valent et al. 2017

	CHIP	CCUS	low-risk MDS	high-risk MDS
Monoclonal/Oligoclonal	+	+	+	+
Cytopenia	-	+	+	+
Dysplasia	-	-	+	+
BM blasts	<5%	<5%	<5%	<20%
Flow abnormalities	+/-	+/-	++	+++
Cytogenetic aberrations	+/-	+/-	+	++
Molecular aberrations	+	+	++	+++

Clonal hematopoiesis of indeterminate potential - Diagnostics

Cytomorphology

Patients with cardiovascular disease and clonal hematopoiesis of indeterminate potential usually do not show any significant changes in blood count. The red blood cell distribution width (RDW) is on average slightly higher in persons with clonal hematopoiesis of indeterminate potential (CHIP) than in persons without CHIP, but for the individual patient the significance of the RDW value is not sufficient to determine or exclude CHIP without molecular genetic findings. If clonal hematopoiesis is present on the basis of the molecular genetic findings, a differentiation of CHIP (absence of dysplasia and cytopenia) from CCUS (cytopenia but absence of dysplasia) or myeloid neoplasia should be made in the course of a cytomorphological examination. If the blood count shows evidence of dysplasia or cytopenia, further haematological clarification is recommended (see **Clonal haematopoiesis of indeterminate potential (CHIP) in hamatology**).

Molecular genetics

In cardiac patients without suspected hematologic neoplasia, molecular genetic detection of somatic mutations in the peripheral blood is the key finding to detect the presence of clonal hematopoiesis of indeterminate potential (CHIP). For this purpose, recurrently mutated genes are sequenced using Next-Generation-Sequencing (NGS) (Hoermann et al. 2020).

The distinction between CHIP, CCUS and MDS cannot be made on the basis of molecular genetic examinations, but is currently based on differences in the presence of cytopenia and, for MDS, diagnostic morphological or cytogenetic criteria (see also Table 1).

A smooth transition between clonal hematopoiesis of indeterminate potential , CCUS and MDS is assumed to be likely (Bejar Leukemia 2017). Thereby, the genetic complexity with regard to the mutation load and the number of mutations increases (Cargo et al. 2015, Bejar Curr Opin Hematol. 2017, Malcovati et al. 2017, Bewersdorf et al. 2019). The genes mutated in CCUS correspond to those also affected in CHIP and MDS. However, the mutation landscapes differ with regard to the frequently occurring mutations (see Table 2) (Bejar Curr Opin Hematol. 2017).

Table 2: Comparison of genetic characteristics between CHIP, CCUS and MDS, according to Bejar Curr Opin Hematol. 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%

Compared to CCUS, MDS is more complex in molecular genetic terms: there are usually two or more mutations and the mutation load is usually more than 10% (Haferlach et al. 2014, Malcovati et al. 2017, Sperling et al. 2017). Since mutations accumulate during progression, it is recommended that investigations be carried out during the course of the progression in question cases (e.g. Steensma et al. 2015).

CHIP cardiology - Recommendation

CHIP can be an incidental finding from a person's DNA sequencing for hematological, oncological or medical-genetic reasons and requires joint hematological and cardiological management (Bolton et al. 2020).

From a cardiological point of view, screening for the presence of CHIP in cardiologis currently not generally recommended, as there is not yet sufficient evidence for the specific treatment of cardiovascular risk in patients with CHIP. The indication for a molecular genetic analysis for the presence of CHIP should therefore only be made in individual cardiac patients when the risk situation is unclear (Jaiswal et al. 2020). At present, CHIP-associated risk is still not included in traditional cardiovascular risk models, although it is at least of a similar order of magnitude to established cardiovascular risk factors such as smoking, hyperlipidaemia or hypertension. Currently, there is still a lack of evidence-based recommendations or therapies aimed at specifically reducing the CHIP-associated cardiovascular risk. Cardiovascular management of patients with CHIP is therefore based on individualised risk assessment and counselling to generate awareness among patients and mitigating the overall cardiovascular risk by guideline-based primary and secondary prevention (Bolton et al. 2020; Jaiswal et al. 2020).

For haematological management, a differential blood count is recommended at regular intervals (initially after 3 months, later every 12 months) in patients with clonal hematopoiesis of indeterminate potential and normal blood count to assess possible progression (Heuser et al. 2016). If a patient with CHIP develops peripheral cytopenia of unclear cause, further hematological assessment including bone marrow puncture is recommended initially and subsequently a differential blood count after 1, 2 and 3 months and subsequently every 3 months (Heuser et al. 2016, see also **Clonal hematopoiesis of indeterminate potential (CHIP) in hematology**).

References

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