Clonal hematopoiesis of indeterminate potential (CHIP in cardiology)

Status: May 2020

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Anticoagulant</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomorphology</td>
<td>EDTA</td>
<td>mandatory in case of positive molecular genetics</td>
</tr>
<tr>
<td>Immunophenotyping</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>Chromosome analysis</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>FISH</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>Molecular genetics</td>
<td>EDTA or Heparin</td>
<td>mandatory</td>
</tr>
</tbody>
</table>
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 hematopoiesis has been detected in about 10% of persons from the age of 70 onwards. Similar to patients with MCLUS (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 CHIP than in background. A clonal hematopoiesis of indeterminate potential was introduced as a new term only a few years ago. Clonal hematopoiesis of indeterminate potential was shown in animal models of a total of more than 40,000 DNA samples from peripheral blood not selected for hematological diseases to reveal 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, hypertension (Jaiswal et al. 2019). 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 causes an inflammatory phenotype has been described for 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 heart failure after successful revascularization of myocardial infarction. CHIP was frequently detected in this patient group (8.5%) 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<0.003). 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) (Chornemier et al. 2019). Again, a causal relationship between TET2 mutated or deficient proinflammatory 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).

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 inauspicious 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 altered.

Characteristics of clonal hematopoiesis of indeterminate potential (CHIP)

(according to Steensma et al. 2015)
- Evidence of clonal hematopoiesis
- Absence of dysplasia of hematopoiesis in bone marrow
- No proliferation of blasts in bone marrow
- Inclusion of parapsidal nodular haemoglobinuria (PNH), MGUS and MBL
- Progression rate of 0.5-1% per year

*Somatic mutation with an allelic frequency of at least 20% in any of the genes: DNMT3A, TET2, JAK2, SF3B1, ASXL1, TP53, CBL, CBL1, BCR, CASP1, CREBB, CUX1, SRSF2, ML2 (KMT2D), SETD2, SETD1B, ONAS, PPM1D, BCR1 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 hematopoiesis is accompanied by cytopenia, it 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 (Hafnerl 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 (Jaiswal et al. 2017).
Table 1: Distinction of CHIP and CCUS from MDS, modified according to Valent et al. 2017

<table>
<thead>
<tr>
<th></th>
<th>CHIP</th>
<th>CCUS</th>
<th>low-risk MDS</th>
<th>high-risk MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal/Oligoclonal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BM blasts</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Flow abnormalities</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Cytogenetic aberrations</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Molecular aberrations</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

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 hematopoiesis of indeterminate potential (CHIP) in haematology).

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).
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 cardiology is 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 cardiological cases 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.mli.com/en/diagnostic-offer/other/clonal-hematopoiesis-of-indeterminate-potential-chip-in-cardiology.html#references