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OCCULT HEPATITIS C VIRUS INFECTION IN ACUTE AND CHRONIC MYELOID LEUKEMIA

Seham Mahrous [1], Ahmad Baraka [1], Ayman Fathy [1] and Madonna Fayez [1*]

[1]*Depratment of Clinical Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt.*

Abstract

A widely used definition of Occult Hepatitis C Virus Infection (OCI) is the presence of HCV RNA in hepatocytes or peripheral blood mononuclear cells (PBMCs) with undetectable plasma or serum levels of anti-HCV or HCV-RNA serum utilizing current laboratory assays, regardless of hepatic transaminase elevation. there is little information on a possible association between HCV infection and other lymphoid or myeloid malignancies.

Keywords: Occult Hepatitis C Virus, Acute , Chronic Myeloid Leukemia

Introduction :

1. Occult Hepatitis C Virus Infection:

1.1. Definition:

Castillo et al. first described OCI, in 2004 in a group of patients with cryptogenic long-standing abnormal liver-function test results.

A widely used definition of OCI is the presence of HCV RNA in hepatocytes or peripheral blood mononuclear cells (PBMCs) with undetectable plasma or serum levels of anti-HCV or HCV-RNA serum utilizing current laboratory assays, regardless of hepatic transaminase elevation (**Martínez-Rodríguez et al., 2018**).

1.2. Epidemiology :

The prevalence of OCI has been reported in high risk groups to contract HCV. For example, patients with cryptogenic liver disease, the prevalence was reported to be 74.2% (**Rezaee-Zavareh et al., 2015**). In hemodialysis patients, the prevalence ranged between 3.0 to 15.1% (**Naghdi et al., 2017**). In patients without apparent liver disease, the prevalence was reported to be 3.3% (**de Marco et al., 2009**).

1.3. Diagnosis:

Liver biopsy remains the gold standard for diagnosis of OCI by identifying HCV RNA in hepatocytes. However, liver biopsy is not always readily available and it carries risks, such as bleeding or inadvertent puncture of other organs (**Rezaee-Zavareh et al., 2015**).

The diagnosis of these OCI in anti-HCV positive individuals with normal liver enzymes was originally based on investigations of PBMC and plasma but not liver biopsies (P**ham et al., 2012**).

Testing of PBMCs likely underestimates the true prevalence of OCI, as PBMCs will detect only approximately 70% of cases when compared with hepatocyte testing. Serial testing of PBMCs may increase that detection rate if there is high suspicion for OCI (**Austria and Wu, 2018**).

HCV RNA in PBMCs is recommended to detect residual infection in patients with SVR, especially in those with high serum HCV RNA levels before treatment (**Aslan and Altindiş, 2017**).

HCV-RNA in PBMCs and ultracentrifuged serum are alternative diagnostic method for OCI (**Rezaee-Zavareh et al., 2015**).

Ultracentrifugation combined with sensitive RT-PCR effectively demonstrates patients with OCI infection who may have low amounts of viral particles in their sera. By concentrating 2 mL of serum by ultracentrifugation then using HCV RNA detection by RT-PCR, the sensitivity of HCV RNA detection in serum was increased 8-fold. This is in contrast with the standard methods for HCV RNA detection, in which a maximum of 250 µL of serum is used for isolation of RNA (**Austria and Wu, 2018**).

Detection of HCV core antigen in serum or plasma is a promising test which could be an alternative to the molecular techniques, and is particularly important during the window period of HCV infection occurring after HCV infection and before the appearance of antibodies. It can be used as a screening assay for blood or plasma donations in different countries (**Eldaly et al., 2016**).

Combining HCV-RNA detection in PBMCs and in ultracentrifuged serum, along with detection of anti-core HCV , can detect up to 91% of patients that have had proven OCI by liver biopsy (**Castillo et al., 2010**).

Regular RT-PCR is unable to differentiate between positive and negative HCV RNA strands. Therefore, strand-specific RT-PCR was developed to aid in identification and quantification of the negative strand. In strand-specific RT-PCR, a tagged primer specific to the antisense RNA is used, along with other methods meant to increase specificity, such as the use of high temperatures during cDNA synthesis (**Austria and Wu, 2018**).

2. Acute Myeloid Leukemia (AML):

AML is a form of cancer that is characterized by infiltration of the bone marrow (BM), blood and other tissues by proliferative, clonal, abnormally differentiated and occasionally poorly differentiated cells of the hematopoietic system (**Longo et al., 2015**). It consists of a group of relatively well defined hematopoietic neoplasms involving precursor cells committed to the myeloid line of cellular development (i.e., those giving rise to granulocytic, monocytic, erythroid, or megakaryocytic elements) (**Schiffer and Gurbuxani, 2018**).

AML can be divided into two subtypes: de novo, when it is not caused by chemotherapy or another preceding haematological condition, and secondary, when it is derived from such a condition (**Villela and Bolaños-Meade, 2011**).

2.1. Epidemiology:

AML is the most common acute leukemia in adults and accounts for approximately 80 percent of cases in this group. In contrast, AML accounts for less than 10 percent of acute leukemias in children less than 10 years of age (**Smith et al., 2011**).

In adults, the median age at diagnosis is approximately 65 years. The incidence increases with age with approximately 2 and 20 cases per 100,000 population for those under or over 65 years, respectively. The male: female ratio is approximately 5:3, and non-Hispanic Whites have a higher incidence than other racial and ethnic groups (**Noone et al., 2018**).

2.2. Pathogenesis:

AML is a syndrome that includes a heterogeneous group of cancers of blood cells that arise from genetic and epigenetic changes in hematopoietic precursor cells. The malignant cells exhibit abnormal growth and differentiation properties (**Kolitz, 2017**).

AML is maintained by a pool of self-renewing leukemic stem cells that may be more immature than the bulk population of leukemic cells. They are thought to originate from cells with existing self-renewal capacity (ie, hematopoietic stem or progenitor cells) or from progenitors that have re-acquired this stem cell-like property (**Stock and Michael, 2017**).

AML is associated with chromosomal abnormalities, including nonrandom translocations, gain or loss of entire (or portions of) chromosomes, and other karyotypic abnormalities. In some cases, the chromosomal translocations generate chimeric fusion genes that are never expressed in normal cells. As an example, in acute promyelocytic leukemia (APL), a chromosomal translocation juxtaposes the Retinoic Acid Receptor Alpha (RARA) locus on chromosome 17 and the promyelocytic leukemia gene on chromosome 15 to generate the chimeric PML-RARA oncoprotein (**Kumar, 2011**).

In addition, key regulators of cellular growth and differentiation are altered by point mutations and small duplications or deletions of genes that are not detectable on routine karyotyping (**Stock and Michael, 2017**).

2.3. Clinical presentation:

Patients with AML generally present with symptoms related to complications of pancytopenia (e.g., anemia, neutropenia, and thrombocytopenia), including weakness and easy fatigability, infections of variable severity, and/or hemorrhagic findings such as gingival bleeding, ecchymoses, epistaxis, or menorrhagia. Combinations of these symptoms are common (**Schiffer and Gurbuxani, 2017**).

General fatigue is present in the majority of patients and often precedes the diagnosis for a number of months. Also, pallor and weakness are common and attributed to the anemia (**Schiffer and Gurbuxani, 2017**).

Bone pain is infrequent in adults with AML, although some individuals describe sternal discomfort or tenderness, occasionally with aching in the long bones. This may be especially severe in the lower extremities, due to expansion of the medullary cavity by the leukemic process (**Kumar, 2011**).

Occasionally hepatomegaly and/or splenomegaly (<10 percent of patients). Lymphadenopathy is uncommon. Otherwise unexplained headache or focal neurologic complaints (eg, due to central nervous system hemorrhage or leukemic meningitis) (**Shephard et al., 2016**).

It is generally difficult to precisely date the onset of AML, at least in part because individuals have different symptomatic thresholds for choosing to seek medical attention. It is likely that most patients have had more subtle evidence of BM involvement for weeks, or perhaps months, before diagnosis (**Schiffer and Gurbuxani, 2017**).

If untreated, AML is usually fatal within weeks from the time of diagnosis (**Villela and Bolaños-Meade, 2011**).

2.4. Diagnosis and classification:

AML should be suspected in any individual with circulating blast cells (immature myeloid cells), unexplained cytopenias, and/or related symptoms, and certain unexplained metabolic/oncologic emergencies (eg, tumor lysis syndrome, hyperleukocytosis). Such patients should be referred urgently for expert evaluation and management (**Kolitz, 2017**).

A complete diagnosis of acute leukemia requires knowledge of clinical information combined with morphologic evaluation, immunophenotyping and karyotype analysis, and often, genetic testing.

Cooperation between clinicians and pathologists is key to ensuring an accurate diagnosis (**Arber et al., 2017**).

Although a presumptive diagnosis of AML can be made via examination of the peripheral blood smear when there are circulating leukemic blasts, a definitive diagnosis usually requires an adequate BM aspiration and biopsy. BM trephine biopsy is considered in patients with dry tap on aspiration, due to the presence of a hypercellular marrow packed with blasts, or extensive fibrosis (**Schiffer and Gurbuxani, 2017**).

BM aspirate and biopsy, including morphology, immune-phenotype, cytochemistry and genetics studies (conventional karyotype and molecular studies) remain essential for diagnosis, classification and risk stratification (**Saultz and Garzon, 2016**).

Criteria for the diagnosis of AML include the following (**Döhner et al., 2017**):

- Blast forms must account for at least 20 percent of the total cellularity of the BM biopsy sample or the peripheral white blood cell count. Exceptions that are considered diagnostic of AML without regard to the BM blast count include leukemias with certain specific genetic abnormalities, myeloid sarcoma, and central nervous system involvement with myeloblasts.

- The blast forms must be identified as cells of the myeloid lineage, as distinct from the lymphoid lineage. Most often, the presence of myeloid antigens on the blast cell surface is detected by flow cytometry. Presence of Auer rods (needle-like filaments of primary granules) is a feature of AML.

Following diagnosis, AML is classified using the WHO classification system based upon a combination of morphology, immunophenotype, genetics and clinical features. The classification attempts to identify biologic entities in the hopes that future work will elucidate molecular pathways that might be amenable to targeted therapies (**Arber et al., 2016**).

There are six main groups of AML recognized in this classification system (**De Kouchkovsky and Abdul-Hay, 2016**):

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related features
- Therapy-related AML and myelodysplastic syndrome (MDS)
- AML, not otherwise specified
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome

WHO category "AML with recurrent genetic abnormalities" accounts for approximately 20 to 30 percent of AML cases. It contains the most common AML variants that contain distinct genetic abnormalities of prognostic significance. Other chromosomal or molecular abnormalities can be present in addition to the primary defining genetic abnormality in some patients. There are nine defined structural or molecular abnormalities that define specific AML subtypes and two provisional entities identified at the molecular level (AML with mutated RUNX1 and AML with BCR-ABL1) (**Dores et al., 2012**). APL is a biologically and clinically distinct variant of AML. In the WHO classification system, APL is classified as acute promyelocytic leukemia with PML-RARA. It accounts for up to 13 percent of newly diagnosed AML (**Grimwade et al., 2010**).

AML with myelodysplasia related features (previously called AML with multilineage dysplasia) includes cases that fit the criteria for a diagnosis of AML (≥20 percent blasts) without a history of prior cytotoxic therapy (**Arber et al., 2016**).

The diagnosis of therapy related myeloid neoplasm is made when AML, MDS, or MDS/myeloproliferative neoplasm (MPN) is diagnosed in a patient with prior exposure to cytotoxic agents (**Schiffer and Gurbuxani, 2018**).

Many cases of AML do not meet the criteria for the documented categories and are classified as AML, not otherwise specified (**Arber et al., 2016**).

2.5. Prognostic Factors:

Clinical features of the patient and cytogenetic/molecular features of the leukemia both contribute to prognosis in AML (**Longo et al., 2015**).

There are several clinical findings that may help predict the likelihood of attaining a complete remission (CR) and subsequent disease-free survival in patients with AML. The strongest adverse clinical predictors are advanced age, poor performance status, cytogenetic and/or molecular genetic findings in tumor cells, history of prior exposure to cytotoxic agents or radiation therapy and history of prior myelodysplasia or other hematologic disorders such as MPNs (**Döhner et al., 2017**).

The European Leukemia Net integrates cytogenetic and molecular features in AML to divide cases into three prognostic risk groups that differ based on rates of complete remission, disease free survival, and overall survival (**Döhner et al., 2017**).

The five years overall survival rate ranges from 40% to 50% in patients aged <60 years and from 20% to 30% in patients aged >60 to 70 years who receive high intensity chemotherapy regimens (**Medeiros et al., 2019**).

3.Chronic Myeloid Leukemia (CML):

CML is MPN characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation. It is also known as chronic myelocytic, chronic myelogenous, or chronic granulocytic leukemia (**Richard A Van Etten, 2017**).

CML is a clonal hematopoietic stem cell disorder that results in increases in not only myeloid cells but also erythroid cells and platelets in peripheral blood and marked myeloid hyperplasia in the bone marrow (**Khaled and Abd El Aziz, 2015**).

The clinical hallmark of CML is the uncontrolled production of mature and maturing granulocytes, predominantly neutrophils, but also basophils and eosinophils (**Richard A Van Etten, 2017**).

2.6 Pathogenesis:

CML is associated with the fusion of the Abelson murine leukemia (ABL1) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22. This results in expression of an oncoprotein termed BCR-ABL1. This abnormal fusion typically results from a reciprocal translocation between chromosomes 9 and 22 that gives rise to an abnormal chromosome 22 called the Philadelphia chromosome. It is this derivative chromosome 22 which harbors the BCR-ABL1 fusion gene (**Thompson et al., 2015**).

BCR-ABL1 is a constitutively active tyrosine kinase that promotes growth and replication through downstream signaling pathways such as RAS, RAF, JUN kinase, MYC, and STAT. This influences

leukemogenesis by creating a cytokine independent cell cycle with aberrant apoptotic signals in response to cytokine withdrawal (**Jabbour and Kantarjian, 2018**).

2.6 Epidemiology and risk factors:

CML accounts for approximately 15 to 20 percent of leukemias in adults (**Siegel et al., 2017**). It has an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance (**Smith et al., 2011**). The median age at presentation is approximately 50 years for patients enrolled on clinical studies, but the actual median age from cancer registry data may be 10 years older. Exposure to ionizing radiation is the only known risk factor (**Richard A Van Etten, 2017**).

While there is no known familial disposition to CML (**Björkholm et al., 2013**), rare families in which multiple members develop MPNs, including CML, have been described. Studies of these families suggest the presence of an autosomal dominant mutation that may predispose to acquisition of a secondary somatic mutation such as the Philadelphia chromosome translocation or JAK2 mutation (**Kim et al., 2011**).

The prevalence of CML is steadily increasing in the western world due to the dramatic effect of ABL1 kinase inhibitors on survival. It is estimated that there will be >180,000 patients living with CML in the US by the year 2050 (**Huang et al. 2012**).

2.6. **Clinical presentation*:***

About 50% of patients diagnosed with CML in the United States are asymptomatic, and are often diagnosed during a routine physical examination or blood tests (**Thompson et al., 2015**).

The symptoms of CML are often vague and can happen with other cancers, as well as with many conditions that aren't cancer (**American cancer society, 2017**).

Among symptomatic patients, systemic symptoms such as fatigue, malaise, weight loss, excessive sweating, abdominal fullness, and bleeding episodes due to platelet dysfunction are common. Also, abdominal pain and discomfort may include left upper quadrant pain and early satiety, due to the enlarged spleen with or without perisplenitis and/or splenic infarction. Tenderness over the lower sternum, due to an expanding bone marrow, is sometimes seen. Acute gouty arthritis may also present at this time, due to overproduction of uric acid (**Jabbour and Kantarjian, 2018**).

Other frequent findings include splenomegaly (present in 48 and 76 percent in two series), anemia (45 and 62 percent), white blood cell count above 100,000/microL (52 and 72 percent), and platelet count above 600,000 to 700,000/microL (15 and 34 percent). Involvement of extramedullary tissues such as the lymph nodes, skin, and soft tissues is generally limited to patients with blast crisis (**Richard A Van Etten, 2017**).

Many of the signs and symptoms of CML occur because the leukemia cells replace the bone marrow's normal blood making cells. As a result, people with CML don't make enough red blood cells, properly functioning white blood cells, and platelets (American cancer society, 2017).

2.7. Diagnostic tests:

The peripheral blood smear typically demonstrates absolute leukocytosis (median of 100,000/μL) with a left shift and classic “myelocyte bulge or leukemic hiatus” (more myelocytes than the more mature metamyelocytes seen on the blood smear), blasts usually number <2%, absolute basophilia is nearly universal, with absolute eosinophilia in 90% of cases. Monocytosis is often seen, but generally not an increased monocyte percentage, absolute monocytosis is more prominent in the unusual cases with a

p190 BCR-ABL. Platelet count is usually normal or elevated, thrombocytopenia suggests an alternative diagnosis or the presence of advanced stage, rather than chronic phase disease (**Thompson et al., 2015**).

BM aspiration and biopsy demonstrates granulocytic hyperplasia with a maturation pattern that reflects that seen in the peripheral smear. Other non-specific BM findings include an increase in reticulin fibrosis and vascularity (**Hidalgo-Lopez et al., 2017**).

Conventional cytogenetics looks at chromosomes (pieces of DNA) under a microscope to find any changes. It's also called a karyotype. Because chromosomes can best be seen when the cell is dividing, a sample of blood or BM has to be grown so that the cells start to divide. This takes time, and doesn't always work (**American cancer society, 2017**).

A fluorescence in situ hybridization (FISH) analysis relies on the colocalization of large genomic probes specific to the BCR and ABL genes. Comparison of simultaneous BM and blood samples by FISH analysis shows high concordance. FISH studies may have a false positive range of 1%-5% depending on the probes used (**Jabbour and Kantarjian, 2018**).

Reverse transcriptase PCR (RT-PCR) amplifies the region around the splice junction between BCR and ABL1. It is highly sensitive in detecting minimal residual disease. PCR testing can either be qualitative providing information about the presence of the BCR-ABL1 transcript for diagnosing CML, or quantitative assessing the amount of BCR-ABL1 transcripts for monitoring residual disease. Simultaneous peripheral blood and BM qualitative PCR studies show a high level of concordance (**Jabbour and Kantarjian, 2018**).

2.8. Diagnosis:

The diagnosis of CML is first suspected by identifying the typical findings in the blood and BM, and then confirmed by the demonstration of the Philadelphia chromosome, the BCR-ABL1 fusion gene or the BCR-ABL1 fusion mRNA by conventional cytogenetics, FISH analysis, or RT- PCR (**Arber et al., 2016**).

Hydroxyurea can be used to reduce white blood cell counts while awaiting confirmation of a suspected diagnosis of CML in a patient with significant leukocytosis (eg, >80 x109 white cells/L) (**Richard A Van Etten, 2017**).

2.9. Disease phases:

Patients with CML can present in one of three general disease phases (**Richard A Van Etten, 2017**):

- Chronic phase, which is present at the time of diagnosis in approximately 85 percent of patients.
- Accelerated phase, in which neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control with treatment.
- Blast crisis, a condition resembling acute leukemia in which myeloid or lymphoid blasts proliferate in an uncontrolled manner.

WHO defines accelerated phase as patients with CML who show one or more of the following features (**Furtado et al., 2015**):

- 10 to 19 percent blasts in the peripheral blood or BM.
- Peripheral blood basophils ≥20 percent.
- Platelets <100,000/microL, unrelated to therapy.
- Platelets >1,000,000/microL, unresponsive to therapy.
- Progressive splenomegaly and increasing white cell count, unresponsive to therapy.

- Cytogenetic evolution (defined as the development of chromosomal abnormalities in addition to the Philadelphia chromosome).

The blastic phase is usually defined by the presence of one or more of the following findings (**Thompson et al., 2015**):

- ≥20 percent peripheral blood or BM blasts.
- Large foci or clusters of blasts on the BM biopsy.
- Presence of extramedullary blastic infiltrates (eg, myeloid sarcoma, also known as granulocytic sarcoma or chloroma).

3. OCI in patients with hematological cancers:

Studies of the association between OCI and hematological disorders have yielded controversial results (**Kisiel et al., 2014**).

OCI are a significant clinical problem in patients with hematological disorders, warranting wider use of molecular tests combined with periodic evaluations of liver functions for diagnostic purposes (**Helaly et al., 2017**).

OCI occurs in Egyptian patients with lymphoproliferative disorders at a prevalence of 20% compared to 26% of HCV (**Youssef et al., 2012**).

On the other hand ***Coppola et al. (2011)***, shows that neither occult HCV infection nor its reactivation under strong immunosuppressive chemotherapy were found in oncohematological patients who were anti-HCV and HCV RNA negative

Liver biopsy remains the gold standard for diagnosis of OCI by identifying HCV RNA in hepatocytes. However, liver biopsy is not always readily available and it carries risks, such as bleeding or inadvertent puncture of other organs

CONFLICTS OF INTEREST :

The authors have no conflicts of interest to declare.

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