HBV Reactivation: A Preventable Menace

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Disclosures

• Research Grant Support
  – Gilead
  – BMS
Case Presentation

- 38F HBsAg+ with newly dx’d breast CA
  - poorly differentiated infiltrating ductal CA
- Recommendation made for immediate chemotherapy followed by surgery
- HBsAg+ known since age 24
- SH: emigrated from Shanghai, married with 3 yo child, works as chemist
- Labs: LFTs WNL, CBC, INR normal, HBsAg(+), eAg(-), HBV DNA < 60 IU/mL
Case Presentation

• Begun on preoperative Doxorubicin/Cyclo
  – LFTs normal pre-treatment and after first 3 cycles
• After 4th cycle: AST 3800, ALT 900, LDH 1800, TB 1.7, admitted to OSH
• 3 days later (6.23.07): TB 20/DB 13.5, AST 298, ALT 312, INR 5.2, NH₃ 47 → 122, transferred to MGH
• ETV 1 mg/d begun, HBV DNA 4.0x10¹⁰ IU/mL
• ALT, AST improved, but INR rose to 15, HE worsened, NH₃ to 160
• Listed status I for OLT 7.3.07 → OLT 7.7.07
• 2017: has done well on ETV since, NED
HBV Reactivation

- A significant and underappreciated problem
- Completely preventable with appropriate preparation
- Clinical scenarios:
  - Chemotherapy
  - Immunosuppression
  - Biologics
  - Cure of HCV with DAAs
Hepatitis B Virus

- Small partially double-stranded DNA virus
- Prototype of the *hepadnavirus* family
- 4 major gene products
- glucocorticoid responsive element

![Diagram of Hepatitis B Virus](image)
The HBV lifecycle

Block et al, Antiviral Res 2013 98:27
# Typical Interpretation of Serologic Test Results for HBV Infection

<table>
<thead>
<tr>
<th>Serologic Marker Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBs Ag</td>
<td>Total Anti-HBc</td>
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Natural History of Chronic HBV Infection

Immune tolerance | Immune Clearance | Immune Control (Nonreplicative)

HBV DNA

HBeAg+

HBsAg+

ALT

HBeAg- HBeAb+

HBsAg- HBsAb+

Mos-Yrs

5-30 Yrs

Infection

Natural History of Chronic HBV Infection

**Immune tolerance**
- HBV DNA
- HBeAg+
- HBsAg+
- ALT

**Immune Clearance**
- Immune Control (Nonreplicative)
  - Most Oncology/Rheum Patients
    - Normal ALT
    - Low/undetectable HBV DNA
    - HBsAg+ and HBeAg-
    - or HBsAg-, anti-HBc+

**Immune tolerance**
- HBeAg-
- HBeAb+
- HBsAg-
- HBsAb+

HBV has a latent reservoir

- Immune control—not clearance
- “Resolved HBV” a misnomer—still HBV DNA in liver
- cccDNA—episomal replicative intermediate responsible for persistent infection of hepatocytes

Inactive HBV is controlled by the host immune response

- Immune control—not clearance
- “Resolved HBV” a misnomer—still HBV DNA in liver

Immune Suppression

- Immune control can be lost
- Immune-mediated liver damage with immune reconstitution

HBV Replication Promoted

- Immune control can be lost
- Immune-mediated liver damage with immune reconstitution

Immune reconstitution

- Immune-mediated liver damage with immune reconstitution
HBV Reactivation

- **HBeAg+**
- **HBeAg-**
- **HBeAb+**

**Immunotolerance**

**Immune Clearance**

- **HBV DNA**
- **ALT**

- Infection: 5-30 Yrs
- Mos-Yrs
- Mos-Yrs

HBV Reactivation

- Immunotolerance
- Immune Clearance
- Immune Suppression

HBeAg+

HBeAg-

HBeAb+

HBV DNA

ALT

5-30 Yrs

Mos-Yrs

Mos-Yrs

Infection

HBV Reactivation

- HBeAg+
- HBeAg- HBeAb+
- HBeAg+

Immunotolerance
Immune Clearance

HBV DNA
ALT

5-30 Yrs
Mos-Yrs
Mos-Yrs

Infection

Kinetics of reactivation

Yeo W et al, Hepatology 2006;43:209
HBV Reactivation

**Definition**
- Loss of HBV immune control in a patient with inactive or “resolved” HBV infection
- Abrupt reappearance or increase in viral replication (>1log) with liver damage occurring during and/or following immune reconstitution

**Clinical**
- Range from subclinical to severe/fatal hepatitis
- Rise in HBV DNA ± return of HBeAg
  - may miss HBV DNA spike because HBV DNA may fall with ALT rise
- ALT increase (mild to severe)
- May progress to liver failure/death despite antiviral therapy
## Agents Reported to be Associated with HBV Reactivation

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>High dose dexamethasone, methylprednisolone, prednisolone (very high)</td>
</tr>
<tr>
<td>Antitumor antibiotics</td>
<td>Actinomycin D, bleomycin, daunorubicin, doxorubicin, epirubicin, mitomycin-C (high)</td>
</tr>
<tr>
<td>Plant alkaloids</td>
<td>Vinblastine, vincristine (high)</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Carboplatin, chlorambucil, cisplatin, cyclophosphamide, ifosfamide (high)</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Azauridine, cytarabine, fluouracil, gemcitabine, mercaptopurine, methotrexate, thioguanine (lower)</td>
</tr>
<tr>
<td>Biologics</td>
<td>Alemtuzumab, rituximab (very high)</td>
</tr>
<tr>
<td></td>
<td>Etanercept, infliximab, adalimumab (high)</td>
</tr>
<tr>
<td>Others</td>
<td>L-asparaginase, docetaxel, etoposide, fludarabine, folinic acid, procarbazine (high)</td>
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Oncologic Consequences of Delayed Recognition of HBV Reactivation

Interruption of chemotherapy

- 35% premature termination
- 35% chemo interruption
- Potential for poorer cancer-related outcome

Rate of HBV Reactivation: Solid Tumors

• HBsAg-positive breast cancer patients receiving chemotherapy
  – Rate of HBV-associated acute hepatitis: 21%\textsuperscript{1}
  – With careful HBV DNA monitoring, up to 41% with HBV reactivation\textsuperscript{2}
  – Limited data on other solid tumors

Hematologic Malignancy: The Bigger Threat

100 patients with NHL undergoing CHOP; 27 HBsAg positive

- HBV Reactivation: 48 patients
- Jaundice: 22 patients
- Nonfatal Liver Failure: 4 patients
- Death: 4 patients

Risk Factors for HBV Reactivation

• Malignancy
  – NHL: 40% to 58% of HBsAg+
  – Breast cancer: up to 41% of HBsAg+

• Chemotherapy
  – Prednisone, anthracyclines, rituximab
  – “Potency of immunosuppression”

• HBV DNA
  – HBV DNA $> 3 \times 10^5$ copies/mL
  – Elevated if HBeAg positive

• Demographics
  – Men > women

Steroids Increase Risk of HBV Reactivation

- 50 patients with NHL who were HBsAg+ randomized to epirubicin, cyclophosphamide and etoposide (ACE) ± prednisolone (P)

Who Should Be Screened?

- AASLD recommends screening high-risk individuals
  - Immigrants from endemic areas
    - Asia, Africa, Pacific Islands, Middle East, Eastern Europe, South/Central America, Caribbean, Aboriginal
  - Children of immigrants
  - Men who have sex with men
  - HIV or HCV positive
  - History of IDU, incarceration
  - Hemodialysis

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- CDC, EASL recommend screening of all patients pre-chemo

Few oncologists routinely screen patients initiating chemotherapy for HBV

Self-Reported HBV Screening Practices of 131 US Oncologists

Chart Review of Actual Screening (208 Pts at Single Institution)

What Is the Optimal Screening Strategy?

• Screening all patients is most cost-effective and easiest to implement

• HBsAg should be tested in all individuals, with follow-up HBV DNA in HBsAg+ patients

• Role of anti-HBc testing less clear; recommendations from various societies mixed
  – EASL: HBsAg and anti-HBc¹
  – AASLD: HBsAg and anti-HBc²
  – CDC: HBsAg, anti-HBc and anti-HBs³
  – ASCO: Consider HBsAg alone → HBsAg, anti-HBc

Preemptive Antivirals Markedly Diminish HBV Reactivation

- HBsAg-positive patients with NHL treated with CHOP randomized to “preemptive” vs “on-demand” lamivudine

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Choice of Antiviral Therapy and Monitoring

- High barrier compounds recommended
  - ETV or TDF (?TAF)
  - May consider LAM for undetectable or low HBV DNA (<2000 IU/mL), short course chemo

- RTX-based lymphoma therapy: RCT showed ETV superior to LAM (0 vs 13%)

- HBV DNA and ALT should be monitored every 1-3 mos

Timing of Antiviral Therapy

- **When to start**
  - Ideally before or together with chemotherapy
  - Do not delay start of chemotherapy

- **When to stop**
  - If baseline HBV DNA > 2000 IU/mL: high risk of withdrawal flare
    - Continue therapy as for chronic HBV infection
  - If baseline HBV DNA < 2000 IU/mL
    - 6-12 mos after end of chemotherapy
    - RTX: 12 mos after last dose

- **Monitor for withdrawal flares with monthly HBV DNA and ALT**

Significance of Isolated Anti-HBc Positivity

• Indicates exposure to HBV
• Usually persists lifelong
• May be false positive if no HBV risk factors
• No guidelines for management
• Risk for reactivation
  – Low risk for most standard solid tumor regimens
  – Consider preemptive HBV therapy if cirrhosis is present
  – Consider preemptive HBV therapy for
    • Rituximab
    • Bone marrow/stem cell transplantation

Rituximab: A Thorny Problem

- Monoclonal antibody against CD20 (B-cell marker)
- Reduces B-cell numbers and neutralizing Ab levels
- Increasingly used as part of CHOP-R, EPOCH-R
- Increased risk of HBV reactivation, including HBsAg-negative (anti-HBc+ +/- anti-HBs) patients
  - High FHF, fatality rates
- **Seroreversion**: reappearance of HBsAg in previously HBsAg-negative patient due to loss of immune control

HBV Reactivation With Rituximab in HBsAg-Negative Individuals

- Patients with diffuse large B-cell lymphoma
  - HBsAg-negative, anti-HBc–positive individuals treated with CHOP or CHOP-R

HBV Reactivation With Rituximab in HBsAg-Negative Individuals

- Patients with diffuse large B-cell lymphoma
  - HBsAg-negative, anti-HBc–positive individuals treated with CHOP or CHOP-R

Among 5 reactivations, 3 -> median of 98 days AFTER last RTX dose
RF: anti-HBs(-), male, age

Recommendations for the anti-HBc+ (+/- anti-HBs+) patient

• Test for HBV DNA
  – those with detectable HBV DNA should be treated as HBsAg+ patients
  
  – those with undetectable HBV DNA who receive chemotherapy and/or IS should be followed carefully by ALT and HBV DNA testing q1-3 months and treated upon HBV reactivation before ALT elevation (if f/u unreliable -> ppx)

  – preemptive NA therapy in all who receive rituximab and/or combined regimens for hematological malignancies, bone marrow and stem cell transplants
HBV reactivation and DAAs for HCV

- FDA reported 24 cases of HBV reactivation in context of SVR with DAAs
- 22/24 cases HBsAg+ at baseline
- 3 cases FHF → 2 deaths (1 isolated anti-HBc+), 1 LTx
- Occurred during week 4-12 of DAAs
- Precise frequency of reactivation unknown
- ?Competitive relationship between viruses, altered immune milieu after DAAs
**HCV/HBV-coinfected hepatocyte**

- HCV
- HBV
- IFNα/
- IFNλ
- IFNβ
- IFNγ
- Proinflammatory cytokines
- ISGs
- HCV core
- HCV NS5a
- HCV E2
- CD8
- CD4
- NK

+DAAs

- Infectious HCV
- Infectious HBV
- IFNs
- Proinflammatory cytokines
FDA recommendations

• HBV status should be assessed in all pts (HBsAg, anti-HBc)
• Pts with serologic evidence of HBV infection should be followed actively during and after DAA therapy
• Antiviral therapy for HBV should be initiated for HBV as warranted

FDA Update Feb 14, 2017.
Recommendations

• Screening of all patients undergoing chemotherapy or IS should be performed

• Screening is recommended by CDC, EASL, AASLD, and IOM
  – Patients receiving standard chemotherapy, IS
    – Screen HBsAg +/- anti-HBc
  – Patients receiving complex chemotherapy (e.g., rituximab/BMT)
    – Screen HBsAg, anti-HBc, anti-HBs

• Screen all patients receiving DAAs for HCV
• HBV reactivation is preventable!!