Firenze, 13-14 gennaio 2020

Caso Clinico

Riattivazione di HBV in un paziente con linfoma non-Hodgkin in terapia immunosoppressiva

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Caso Clinico

Uomo di razza caucasica di 62 anni con storia di infezioni cutanee recidivanti a carico degli arti inferiori

Settembre 2017: ricovero per erisipela e linfangite coscia sinistra + linfoadenopatia inguinale.

Dicembre 2017: diagnosi di linfoma non-Hodgkin inguinale sinistro.

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Il paziente era seguito presso un ambulatorio di Malattie Infettive per epatopatia cronica HCV correlata genotipo 1b.

Pregressa infezione da HBV (HBsAg pos nel 2010, HBsAg negativo con HBV DNA <20 dal 2012).

Fibroscan di marzo 2017: 7.4kPa.

Eco addome di settembre 2017: nei limiti. Transaminasi mosse. HCV RNA 1.600.000

Ad ottobre 2017 vengono richiesti esami finalizzati ad iniziare terapia con DAA nel gennaio 2018.

A DICEMBRE 2017 DIAGNOSI DI LINFOMA NON-HODGKIN

Esami di febbraio 2018:

HBsAg neg

HBsAb neg

HBcAb pos

Inizio di profilassi con Zeffix

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Il 19/4/2018 inizia chemioterapia con ciclofosfamide, doxorubicina e vincristina (CHOP).

Il 15/5/18 inizia ciclo di rituximab in associazione a CHOP.

Effettua ulteriori due cicli di R-CHOP seguiti da 3 cicli di rituximab **(ultima somministrazione il 19/9/18**).

Cicli di Medrol 16 mg die

Al controllo di ottobre 2018 paziente in remissione di malattia.

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Il paziente viene rivisto in ambulatorio di Malattie Infettive a dicembre 2018. Transaminasi mosse, HCV RNA 1.610.000. Fibroscan: 13.6 kPa. HBV DNA <20

Alla visita del 15 gennaio 2019: ECO addome nei limiti. Viene riprogrammato un controllo alla fine del mese con successiva vista per inizio DAA.

Il 26/1/2019 inizia EPCLUSA per 12 settimane.

Al controllo dell' 19/2/19 transaminasi nella norma e HCV RNA<15.

Alla visita del 16/4/19 viene riferita astenia, comparsa da circa una decina di giorni, associata a ipertransaminasemia (ALT 236). Il controllo del 12/4 mostra AST 696, ALT 1030, **HBsAg pos (46), HBV DNA 547.000**

Il paziente ha smesso di assumere Zeffix dalla metà di gennaio.

RICOVERO IN MALATTIE INFETTIVE 16/4/2019

Inizia terapia con entecavir 0.5 mg

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Esami ematici del 17/4/19:
AST 1456
ALT 2000
GGT 256
AMMONIO 115
BIL TOT 0,95- DIR 0,39
HBsAg pos
HBsAb neg
HBeAg neg
HBeAb pos
HBV DNA 69.400
HAV IgM neg
HEV IgG/IgM neg; HDV Ab neg
HIV neg

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Il paziente mostra un peggioramento degli esami fino al 20/4 con successivo miglioramento e declino degli indici di citolisi epatica a partire dal 22/4. Alla dimissione, il 26/4, AST 145, ALT 583, Ammonio 95. Il paziente viene riaffidato a servizio di Malattie Infettive inviante.

Il 21/4/19 ha concluso le 12 settimane di trattamento con Epclusa

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Ricovero il 15/10 in neurochirurgia a Careggi per ESA temporo-parietale con aneurisma sacciforme al tratto terminale del sifone carotideo sx. Eseguita embolizzazione con spirali dell'aneurisma. Dimesso il 27/5/19.

Al controllo di agosto 2019: HCV RNA <15; HBV DNA< 20, **HBsAg neg** con HBsAb neg

Al controllo di novembre 2019: **HBsAg neg, HBsAb 8.4,** HBV DNA <20; : HCV RNA <15;

Il paziente sta continuando profilassi con entecavir 0.5 mg.

Linfoma in remissione.

Patients undergoing immunosuppressive therapy or chemotherapy

Recommendations

- All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression (Evidence level I, grade of recommendation 1).
- All HBsAg-positive patients should receive ETV or TDF or TAF as treatment or prophylaxis (Evidence level II-2, grade of recommendation 1).
- HBsAg-negative, anti-HBc positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation (Evidence level II-2, grade of recommendation 1).

In HBsAg-positive and HBsAg-negative, anti-HBc positive patients receiving chemotherapy or immunosuppressive therapy…the risk of HBV reactivation can be high, particularly if rituximab is given alone or in combination with steroids.1 The risk of HBV reactivation can be classified as high (>10%), moderate (1–10%) or low (<1%).Therefore, all candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg, anti-HBs and anti-HBc prior to immunosuppression treatment.

Table 2. Risk estimates of HBV reactivation according to drug class[109,110]

Risk estimate of HBV reactivation	Drug class	Drug
High (>10%)	B-cell depleting agents	Rituximab (anti-CD20) Ofatumumab (anti-CD20)
	Anthracycline derivatives	Doxorubicin Epirubicin
	Corticosteroids	High dose eg prednisone ≥20 mg for ≥4 weeks
Moderate (1-10%)	TNFa inhibitors	Infliximab Etanercept Adalimumab
	Cytokine inhibitors and Integrin inhibitors	Abatacept (anti-CD80, -86) Ustekinimab (anti-IL12, -23) Natalizumab (binds α4-integrin) Vedolizumab (binds integrin $\alpha_4\beta_7$ [LPAM-1])
	Tyrosine kinase inhibitors	Imantinib Nilotinib
	Corticosteroids	Moderate dose eg prednisone <20 mg for ≥4 week
Low (<1%)	Corticosteroids	Low dose eg prednisone for <1 week
	Corticosteroids	Intra-articular corticosteroids
	Traditional immunosuppression	Azathioprine 6-mercaptopurine Methotrexate

HBV, hepatitis B virus.
TNF, tumour necrosis factor; IL, interleukin; LPAM, lymphocyte Peyer's patch adhesion molecule.

Table 1. Incidence of Hepatitis B reactivation due to immunosuppression according to disease

Disease	Incidence of HBV reactivation without HBV prophylaxis		References
	HBsAg positive (%)	HBsAg negative/anti-HBc positive (%)	
Lymphoma	18-73	34-68	6, 10, 33, 51-53
Acute leukaemias	61	2.8-12.5	31, 32
Chronic leukaemias	NA*	NA*	NA*
Multiple myeloma	NA	6.8-8	24, 47
Bone marrow/haematopoetic stem cell transplantation	66-81	6-10	13, 59, 61
Breast cancer	21-41	NA	14, 134, 157, 158
Nasopharyngeal cancer	33	NA	66
Hepatocellular cancer (systemic chemotherapy)	36	11	68, 159
Hepatocellular cancer (trans-arterial chemoembolization)	21-30	9.3	71-73
Rheumatoid arthritis	12.3	3-5	160-163
Psoriasis/psoriatic arthritis	NA*	NA*	NA*
Inflammatory bowel disease	36	0-7*	80, 81
Autoimmune diseases	NA*	17*	92
Renal Transplantation	45-70	0.9	93, 97-99

HBV, hepatitis B virus; NA, not available..

*Case reports or small case series reporting HBV reactivation.

Table 3. Summary of American Gastroenterology Association guidelines on the prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy[109, 110]

Population at risk of HBV reactivation	Screening test	Is antiviral prophylaxis recommended?		Antiviral drug recommended for prophylaxis	Monitoring in untreated HBsAg negative/anti-HBc positive patients
		HBsAg positive	HBsAg negative/ anti-HBc positive		
High risk of HBV reactivation (>10%) • B-cell depleting agents • Anthracycline derivatives • High dose corticosteroids (≥20 mg prednisone for ≥4 weeks)	HBsAg and anti-HBc; HBV DNA if serology +ve	Yes (B1) Continue at least 6 months after completion of chemotherapy and at least 12 months for B-cell depleting agents	Yes (B1) if taking: • B-cell depleting agents • Anthracycline derivatives Continue until at least 12 months after completion of chemotherapy for B-cell depleting agents	Drug with high barrier to resistance is favoured over lamivudine (B2).	No recommendation provided
Moderate risk of HBV reactivation (1-10%) • TNFa inhibitors • Cytokine or Integrin inhibitors • Tyrosine kinase inhibitors • High dose corticosteroids (≥20 mg prednisone for ≥4 weeks)	HBsAg and anti-HBc; HBV DNA if serology +ve	Yes (B2) Continue until at least 6 months after completion of chemotherapy	Yes (B2) if taking: • TNFa inhibitors • Cytokine or Integrin inhibitors • Tyrosine kinase inhibitors Continue until at least 6 months after completion of chemotherapy	Drug with high barrier to resistance is favoured over lamivudine (B2).	No recommendation provided
Low risk of HBV reactivation (<1%) • Traditional immunosuppression • Intra-articular corticosteroids • Systemic corticosteroids for <1 week	Routine screening not recommended. Screen for HBV as per CDC guidelines[154]; manage accordingly	Not recommended (B2)	Not recommended (B2)	Not applicable	No recommendation provided

Evidence grade A: high quality; B: moderate quality; C: low quality. Recommendation grade 1: strong; 2: weak.
HBV, hepatitis B virus; CDC, center for disease control.

HBsAg-negative, anti-HBc positive subjects. The risk of HBV reactivation in this group varies widely according to the virological profile, underlying disease and the type and duration of immunosuppressive regimen. These subjects can be tested for serum HBV DNA before immunosuppression. If viremic, they should be treated similarly to HBsAg-positive patients. In the high risk group ([10%), including anti-HBc positive subjects who need to be treated with rituximab in the oncohematological setting or those undergoing stem cell transplantation, antiviral prophylaxis is recommended. Prophylaxis should continue for at least 18months after stopping immunosuppression and monitoring should continue for at least 12 months after prophylaxis withdrawal. LAM may be used safely in this setting although few cases of HBV exacerbation due to LAM resistance have been reported. Prophylaxis with ETV or TDF or TAF can be also considered in HBsAg-negative, anti-HBc positive patients receiving highly immunosuppressive regimens of extended duration.

La presenza in pazienti HBcAb positivi di anticorpi anti-HBs sembra avere un ruolo protettivo nei confronti della possible riattivazione di HBV

Paul S, Dickstein A, Saxena A, et al. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: a meta-analysis. Hepatology. 2017;66(2):379–388.

Il trattamento dei pazienti coinfetti HBV/HCV con i DAA può determinare una riattivazione di HBV. Il meccanismo sembra dovuto sia ad un effetto inibitorio diretto di HCV sulla replicazione di HBV, sia alla risposta immune contro HCV che sopprimerebbe anche anche la replicazione di HBV.

De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. J Clin Virol. 2016;78:27–30

Wang C, Ji D, Chen J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. Clin Gastroenterol Hepatol. 2017;15(1):132–136

Calvaruso V, Ferraro D, Licata A, et al. HBV reactivation in patients with HCV/HBV cirrhosis on treatment with direct acting antivirals. J Viral Hepat. 2018;25(1):72–79

Considerazioni

Corretto inquadramento

Gestione multidisciplinare

Counselling e follow-up